ME 8 NUMBER 2

ARCHIVES OF PATHOLOGY

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AUGUST, 1929

PUBLISHED MONTHLY BY THE AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $6.00

Entered as Second-Class Matter [illegible], at the Post Office at Chicago, Illinois, Under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Sec. [illegible] Act of [illegible], 1925.

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VOLUME 8 AUGUST, 1929 NUMBER 2

MUCOID DEGENERATION OF THE OLIGODENDROGLIA AND THE FORMATION OF FREE MUCIN IN THE BRAIN*

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In 1923, Grynfeltt,[1] on studying the central nervous tissues of persons with senile dementia, paralysis agitans and Wilson's disease, found peculiar polylobate patches in the white matter which gave the characteristic histochemical reactions of mucin. At that time, he termed these mucin bodies mucocytes, and thought that they arose from degeneration of microglia cells. Later, Grynfeltt, Pélissier and Pagés [2] demonstrated in their experimental material that a progressive degeneration of the oligodendroglia cells resulted in the accumulation of intracellular mucin, which, on disintegration of the cells, was liberated free into the tissue and tended to coalesce.

The resulting free mucin was identical with the grapelike areas of disintegration reported by Buscaino [3] in 1922. He believed that they had their source in degeneration of myelin sheaths and, less possibly, in degeneration of ganglion cells. Buscaino doubted the mucoid nature of the material and termed it "substance X."

Grynfeltt [4] later produced ependymal lesions in dogs by means of injections of histamine and formic acid and found that progressive degeneration of the subependymal glia cells produced typical grapelike areas, and that the mucin thus produced was discharged into the ventri-

* Submitted for publication, May 17, 1929.

* From the Division of Neurology, Department of Medicine of the University of Chicago and the Douglas Smith Foundation for Medical Research.

1. Grynfeltt, E.: Mucocytes et leur signification dans les processus d'inflammation chronique des centres cérébraux spinaux, Compt. rend. Soc. de biol. **89**: 1264, 1923.

2. Grynfeltt; Pélissier, and Pagés: Demonstration sur la dégénérescence mucocytaire dans les centres nerveux, Bull. Soc. d. sc. méd. et biol. de Montpellier **46**:260, 1924.

3. Buscaino, V. M.: Le cause anatomopathologische della precoxe, Riv. di patol. nerv. **25**:147, 1920 (cited after Ferraro).

4. Grynfeltt, E.: Lésion de l'épendyme dans la dégénérescence mucocytaire des centres nerveux, Bull. Soc. d. sc. méd. et biol. de Montpellier **8**:450, 1927.

cles and could be demonstrated in the spinal fluid. Simon [5] repeated this experimental work and found the same mucoid degeneration of the oligodendroglia in the white matter and deep cortical brain layers. She also found free mucin in the perivascular spaces.

Bailey and Schaltenbrand [6] demonstrated that the acute swelling of oligodendroglia described first by Penfield and Cone,[7] in which the cytoplasm of these cells becomes swollen with a clear, nonstainable fluid, is identical with the mucoid degeneration of Grynfeltt. The acute swelling begins with a fragmentation of the short cell processes, a pyknosis and shrinking of the nucleus, and an increase of the cytoplasm by the imbibition of a nonstaining substance. Eventually, the nucleus is extruded and the cell completely disappears. By means of mucin stains, Bailey and Schaltenbrand demonstrated that the clear fluid filling the cytoplasm was in reality a mucin-like substance.

Bielschowsky [8] and others considered the substances staining like mucin purely as artefacts. Ferraro,[9] however, although not decisively stating that the so-called mucocytes were artefacts, believed that their pathologic significance was doubtful. His two arguments against the conception that they are degenerative products of oligodendroglia are that they can be found in normal brains and that, although the acute swelling of the oligodendroglia cells can be demonstrated easily, mucin cannot be stained in frozen sections. Ferraro could stain mucin-like substances only if alcohol had come in contact with the tissue; consequently he believed that an "alcohol sensitization" was necessary for the demonstration of the "substance X" as mucin. Furthermore, he did not deny the presence of mucin in glia cells or even oligodendroglia, but considered that it was present intracellularly only in phagocytic glia cells which were conveying the mucin from its origin in degenerated myelin sheaths to the blood vessels. That this material was present in oligodendroglia meant that these glia could become phagocytic or gitter cells, a conception which Ferraro [10] attempted to prove, but which has not been confirmed.

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5. Simon, A.: Étude d'histo-pathologic experimentale sur la dégénérescence muqueuse de la névroglie, Thesis, Fac. med. de Montpellier, 1926.

6. Bailey, P., and Schaltenbrand, G.: Die Muköse Degeneration der Oligodendroglia, Deutsche Ztschr. f. Nervenh. **97**:231, 1927. (See this paper for colored plates.)

7. Penfield, W., and Cone: Acute Swelling of Oligodendroglia, Arch. Neurol. & Psychiat. **16**:131 (Aug.) 1926.

8. Bielschowsky, M.: Review of Buscaino's Work, Zentralbl. f. d. ges. Neurol. u. Psychiat., 1927, p. 604.

9. Ferraro, A.: Acute Swelling of the Oligodendroglia and Grapelike Areas of Disintegration, Arch. Neurol. & Psychiat. **20**:1065 (Nov.) 1928.

10. Ferraro, A., and Davidoff, L. M.: The Reaction of Oligodendroglia to Injury of the Brain, Arch. Path. **6**:1030 (Dec.) 1928.

OBSERVATIONS

The human material that we studied consisted of so-called normal brains and pathologic brains in our laboratory collection from cases of uremia, cerebral arteriosclerosis, encephalomalacea, toxic and epidemic encephalitis, Schilder's disease and a variety of other conditions. Sections of tissue embedded in paraffin and celloidin and frozen sections were stained to demonstrate myelin sheaths, axis cylinders, fat, glycogen and connective tissue. The usual hematoxylin-eosin, toluidine blue and Hortega silver carbonate methods were also utilized. A composite

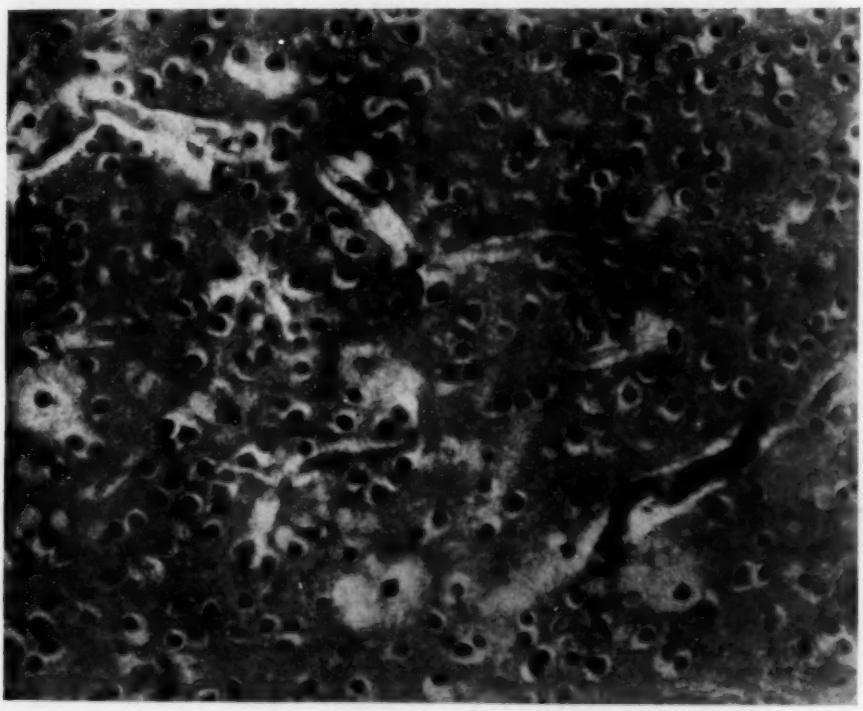

Fig. 1.—Proliferated, swollen oligodendroglia, frequently coalesced. The larger light areas represent mucin free in the tissue and perivascular. Mucicarmine stain; × 390.

description of our observations with all methods and materials will be given.

In most of the brains studied, including the so-called normal ones, acute swelling of the oligodendroglia was found, which is a pathologic condition of a degenerative type. Using this criterion, then, one finds few "normal" brains, for although no important pathologic changes related to the cause of death may be present in the brain, various terminal states, such as fever, dehydration, anoxemia, anemia and agonal states, produce their effect. The oligodendroglia respond to the mildest of

noxious influences by means of active proliferation and acute swelling. These reactions may have a quantitative response to the severity of the toxic process. Therefore, the presence of swollen oligodendroglia and mucinoid degeneration of them in normal brains does not indicate that these changes are artefacts.

In acute toxic encephalitis,[11] for example, the oligodendroglia are massively increased in the white matter of the cerebrum and also as perineural satellitic cells in the cortex. They tend to form streams along the blood vessels, and to the inexperienced their small round nuclei

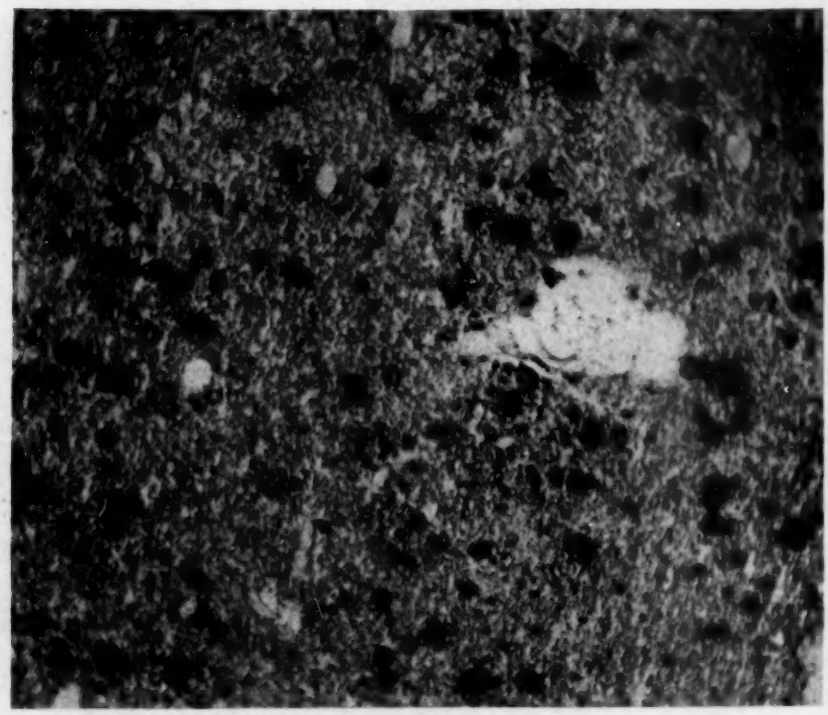

Fig. 2.—Oligodendroglia filled with mucin. The lighter areas are spaces from which free mucin has dropped out of the tissue. Mucicarmine stain.

may even simulate a lymphocytic infiltration. When these proliferated cells swell, even in ordinary nuclear stains the small nuclei may be seen surrounded by a clear, white, circular zone (fig. 1). This appearance is often erroneously interpreted as pericellular edema, but the swelling is within the cell membrane.

In the attempt to stain this cytoplasm, silver impregnations reveal only a colorless fluid embedded in a faint argentophilic reticulum. Fat

11. Grinker, R. R., and Stone, T. T.: Acute Toxic Encephalitis in Childhood, Arch. Neurol. & Psychiat. **20**:244 (Aug.) 1928.

is rarely demonstrated, although an occasional fat granule may be found. No active phagocytosis or formation of gitter cells by the oligodendroglia has been seen by us, although Ferraro contended that such a transition can be shown. Probably his observation represents a fatty degeneration of the cells themselves, although this in itself is extremely rare, being seen by us only once in encephalomyelitis [12] due to rabies vaccine in the form of fine intracellular granules. An attempt at the vital staining of experimentally injured brains of rats has never revealed an oligodendroglia containing dye granules, although the

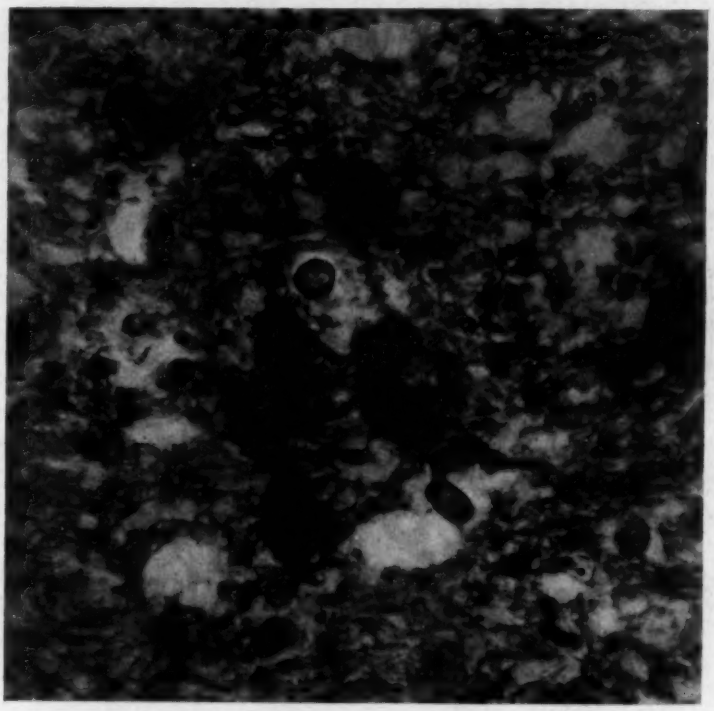

Fig. 3.—An oligodendroglia cell filled with mucin. Mucicarmine stain; × 850.

microglia and their transitional stages to gitter cells contain the vital dye. Therefore, since a phagocytic property of these cells probably does not exist, the picking-up of material which distends the cytoplasm, such as mucin, probably does not occur.

The use of mucicarmine shows that the supposed colorless, swollen cytoplasm stains pinkish red (fig. 2). A metachromatic appearance is found with cresyl violet, and a homogeneous glassy-white appearance

12. Bassoe, P., and Grinker, R. R.: A Clinico-Pathologic Study of Rabies Vaccine Encephalo-Myelitis and Human Rabies, to be published.

with toluidine blue (fig. 5). This stainable substance first appears in an irregular perinuclear ring with delicate strands extending to the cell membrane. Later the mucin-like substance fills the entire cell and, as the cell becomes larger and its surface more irregular, the mucin follows its alteration in shape (fig. 3). The material is not glycogen, since no staining is obtained by Best's method, nor does treating the sections with saliva and subsequent staining of them with mucicarmine alter the appearance.

Fig. 4.—Proliferated, swollen oligodendroglia. The white holes represent mucocytes and are not shrinkage spaces. Van Gieson stain.

The grapelike bodies of Buscaino are numerous. These are large clumps of material in irregular lobulated forms, which stain with mucicarmine. Smaller globules are also present in the tissue, as well as structures of irregular shapes in the midst of nerve fibers. Occasionally, a granular form is seen. The same substance is found in the perivascular and subarachnoid spaces and even within the vessel lumen. Within the grapelike bodies are many swollen oligodendroglia filled with mucin, some of which are only evidenced by a cell membrane, the nucleus being completely degenerated. Mucin clumps identical in shape and size

with clumps of glia cells can be seen, all the nuclei already extended. Coalescing of several oligodendroglia cells filled with mucin, before nuclear degeneration or loss of cell structure have taken place, may be followed to the complete absence of cells and the presence only of free mucin.

Where a globule of mucin is near the surface of the section, pressure on the cover slip results in its loosening from the tissue, leaving a hole. Many of these holes are found, in sections treated with ordinary

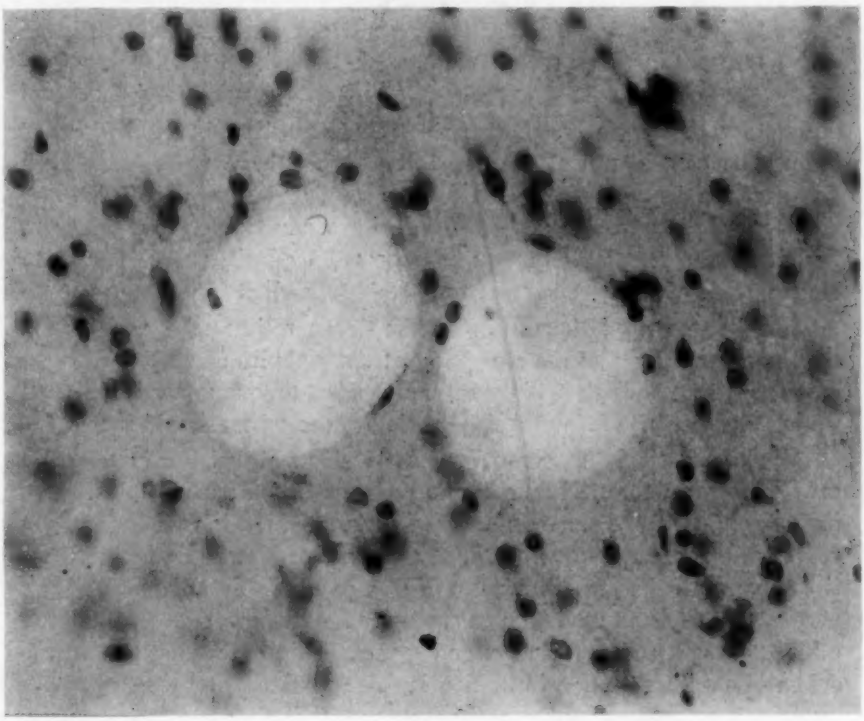

Fig. 5.—Large, homogeneous, glassy globules of mucin. Toluidine blue; × 470.

nuclear stains or with mucicarmine, unstained. They give a sievelike appearance to the section and have been erroneously called tissue spaces due to edema or shrinkage (fig. 4). However, in carefully dehydrated celloidin sections, such an appearance is not found normally. These holes and the stainless cytoplasm of swollen oligodendroglia represent spaces from which mucin has dropped out of the section. The substance is probably only loosely fixed in the cell or the tissue. Correspondingly, smearing the sediment from the bottom of the brain on a slide and staining for mucin shows clearly the globules of mucin which have simply dropped to the bottom of the dish.

Careful examination of the myelin sheaths reveals no evidence of their disintegration. When the mucocytes are found in the white matter, as they grow in size the fibers are simply pushed aside and compressed, but no degeneration is found. No other element, except the oligodendroglia cells themselves, gives any suggestion of partaking in the formation of mucin.

The important point of preparation of the substance X for staining as mucin is easily solved when we find that, without difficulty, mucin can be demonstrated on frozen sections untouched by alcohol. The mucin here is both intracellular and free in the tissue and differs in no way from that in tissue treated with alcohol.

It can be clearly shown that mucin arises in oligodendroglia cells undergoing the regressive change called acute swelling, but which should strictly be called "mucoid degeneration." We have never seen such degeneration in any other type of glia cell, and final proof that the oligodendroglia alone are concerned in its production is our ability to find it in the cytoplasm in tumors reported by Bailey and Bucy [13] to be composed of these cells only, the oligodendrogliomas.

The liberation of the mucin by the degenerating cells, which tend to clump normally, and the coalescing of the globules of mucin form the large grapelike bodies. This substance tends to move toward the blood vessels, along which it is probably carried to the subarachnoid space.

We have used the term mucin rather freely and feel our justification only in the fact that it stains as mucin by so-called mucin stains. The inadequacy of histochemical means of differentiation is well known, yet until more accurate means are at our disposal, we must designate these substances staining with mucicarmine as mucin. The disposal of the mucin, once it is formed, can easily be followed from the degenerating oligodendroglia cell to vascular and subarachnoid spaces, but the mechanism of its intracellular formation is totally unknown.

SUMMARY

Mucoid degeneration and acute swelling of the oligodendroglia represent the same process, which is a specific type of regressive change found in no other glia form. It is not found in normal brains.

The mucin is not formed by degeneration of myelin sheaths or ganglion cells nor is it phagocytosed by the oligodendroglia. It is not artefact, but a product of the oligodendroglia themselves. Alcohol is not a necessary "sensitizer" to bring out the mucin, as ordinary frozen sections stained with mucicarmine reveal the mucin.

13. Bailey, P., and Bucy, P. C.: Tumors of the Brain Composed of Oligodendroglia, J. Path. & Bact., to be published.

Mucocytes form free in the nervous tissue by the liberation of intracellular mucin and its coalescing into grapelike bodies. The mucin eventually reaches the perivascular spaces by which route it is probably conveyed to the subarachnoid space.

The mucin frequently drops out of the tissue and cells, resulting in tissue spaces that are unstainable. This mucin is recoverable from the bottom of the specimen container.

PRENATAL VOLVULUS OF SMALL AND LARGE INTESTINE CAUSED BY A MESENTERIC CYST *

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Cases of mesenteric cyst have been presented from time to time in detail because of the obscurity of their origin and the difficulty of their diagnosis. A wide difference of opinion exists as to their genesis, and a positive diagnosis has probably never been made prior to autopsy or operation. Until lately their significance has not been fully appreciated. Their history has been divided into four periods. The first, from 1507 to 1850, the period of postmortem observations, dates from the first description of a case by the Florentine pathologist Benivieni. The second, from 1850 to 1880, was marked by the occasional accidental finding of one of these cysts at operation, from which no recoveries are reported. During the third period, from 1880 to 1900, there were some cases of recovery after operation in which the cyst had been accidentally found. The fourth and present period, since 1900, has been marked by occasions when the condition has been suspected and a tentative diagnosis made before operation. In our case, no diagnosis of the existing condition was made before death.

REPORT OF CASE

History.—On Aug. 14, 1928, at 10:35 p. m., a female colored child, weighing 7 pounds, 7 ounces (3.7 Kg.) was delivered without difficulty. The infant presented no external abnormalities, and cried lustily. Following its first feeding, however, it vomited greenish fluid. It immediately began to pursue a downward course with vomiting after every feeding. Two days after delivery, the infant no longer fed well, and its skin became cold and clammy. On the third day, bottle feeding was tried, but without benefit. On the fifth day post partum, it vomited a dark-colored fluid. Soon after this jaundice appeared, and the infant died in the evening. The temperature was always between 97 and 98.8 F., but the weight had come down from 7 pounds and 7 ounces (3.7 Kg.) to 6 pounds and 5 ounces (2.6 Kg.). The blood count was as follows: red cells, 3,200,000; hemoglobin, 55 per cent; color index, 0.86; white cells, 21,800; polymorphonuclear neutrophils, 40 per cent; lymphocytes, 45 per cent, and large mononuclears, 15 per cent. The bleeding time was one-half minute and the coagulation time three minutes.

Autopsy.—The autopsy was performed the morning after death. Rigor mortis was complete. The body was emaciated. The fontanels were open and the cranial sutures loose, but there was no craniotabes. The skin, mucous membranes and conjunctivae were jaundiced. The chest was symmetrical. The pleural cavities

* Submitted for publication, May 18, 1929.

* From the Pathologic Laboratory, Harlem Hospital.

contained no free fluid. The lungs were voluminous and hypercrepitant. The visceral pleura was salmon pink, but on section the lungs were moist and dark purplish red. The blood vessels and bronchi were normal. The heart was normal in size, shape and position. The valves were normal; the foramen ovale and the ductus arteriosus were patent. The abdomen was slightly distended, but contained no free fluid. The liver was of usual size but of a dark greenish color. The gallbladder and bile ducts were normal. The spleen was small and firm, and on section the malpighian bodies were visible. The pancreas and the suprarenal glands presented no abnormalities. The kidneys were of usual size; their capsules

Fig. 1.—A "mesenteric" cyst dating from before the fourth month of prenatal life, and causing a volvulus of the small and the large intestine.

stripped easily, disclosing greenish, congested surfaces; several uric acid infarcts were visible. The renal pelves, ureters and bladder were normal.

In the mesentery of the lower jejunum was a large oval cyst, which measured 8 cm. in its longest diameter and was firm. A loop of jejunum lay across its anterior surface and was apparently closely related to it. The jejunum here seemed flattened by pressure of the underlying tumor. Just above the tumor, the small and the large intestine had been involved simultaneously, as illustrated in figure 1, in a volvulus four and one-half turns in a clockwise direction. The

portion of the intestine lying proximal to this was dilated to a diameter of 3.5 cm., while the distal portion measured only 8 mm. in diameter. The cyst and the volvulus were found in the umbilical region of the abdomen. There was no loop of large intestine present on the right side. Although the large intestine was undescended and unrotated, the cecum was not quite of the infantile form. The appendix arose well to the left of its base.

The uterus was small and infantile, three fifths of it consisting of cervix. The rugae were hypertrophied and extended into the corpus. The external os was patent and measured 1 cm. in diameter. The lower third of the cervix dipped into the vagina. The adnexa were normal.

Diagnosis.—Mesenteric cyst, causing prenatal volvulus of the small and the large intestine, with obstruction of the jejunum above the volvulus; undescended large intestine; icterus of viscera, skin and mucous membranes, bilateral lobular pneumonia; patent foramen ovale and ductus arteriosus; uric acid infarcts of the kidneys.

Microscopic Examination.—On section of the cyst, after it was fixed, it was found to contain a slightly cloudy yellowish fluid, which flowed freely. The inner wall of the cyst felt velvety, and that portion of its dome adjacent to the underlying intestine appeared to be continuous with the intestine. Microscopically, the cyst wall consisted of four coats, mucosa, submucosa, two layers of muscularis and a serosa, exactly as in the intestinal canal proper. Throughout the circumference, the inner circular and the outer longitudinal layers of smooth muscle were distinctly demarcated and well developed, being arranged at right angles to each other as in the adjacent intestine. At the junction of cyst and bowel, however, the inner circular layer of the cyst divided into two portions which encircled the intestine and formed the latter's inner circular layer. The layer of muscle between intestine and cyst was common to both; the wall at this point from the lumen of the cyst to the intestinal lumen consisted of mucosa of cyst, submucosa, circular muscle, submucosa and mucosa of intestine. The external longitudinal muscle layer was common to both cyst and intestine. The mucosa of the intestine adjacent to the cyst was somewhat altered by pressure of the cyst. The villi were flattened and, microscopically, the mucosa was changed abruptly. Over this area, the mucosa was flattened and the glands were reduced in number; here the high columnar cells were more cuboidal and the nuclei more uniformly circular and crowded. The mucosa of the cyst was exactly similar to the mucosa of the flattened base of the adjacent intestine just described, except at the common septum, where it was much thinner than elsewhere and for short distances even appeared to be flattened completely. Apparently, the pressure from the overdistended cyst acting on the septum between the lumen of the bowel and that of the cyst, which was naturally its weakest point because of the absence of a portion of the muscular envelope present elsewhere, accounts satisfactorily for the stretching of the septum producing the change in the cyst and the bowel just described (fig. 2).

COMMENT

Two cases of prenatal volvulus due to so-called mesenteric cyst have been described in the literature in the past fifteen years. In these cases, the volvulus involved only the small intestine, and operative procedure was resorted to in both, but without success. These cases have been referred to as rare, if not unique. Our case may be considered still more unusual in that an undescended large intestine, together with the

small intestine, was involved in the volvulus. The microscopic observations already mentioned, moreover, may serve to clear up the problem of etiology and point out a fallacy in the surgical treatment.

Moynihan's [1] classification (1897) of cysts is probably the first comprehensive one, namely: (1) serous, (2) chylous, (3) hydatid, (4) blood, (5) dermoid and (6) cystic malignant disease. Only one group in this list suggests an embryonic origin.

In 1900, Dowd,[2] in discussing a case of multilocular cystadenoma of the transverse mesocolon, resembling a cystadenoma of the ovary, suggested its probable origin as an embryonic ovarian sequestration and proposed this classification: (1) embryonic cysts, (2) hydatid cysts and (3) cystic malignant disease. In doing so, he also suggested that chylous, sanguineous and serous cysts are merely the result of effusion of these characteristic fluids into preformed cysts, and he made the

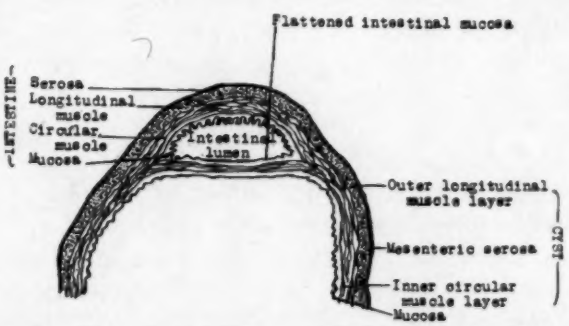

Fig. 2.—Diagram of a transverse section through the "mesenteric" cyst of figure 1. It shows the cyst invaginated between leaves of the mesentery of the small intestine.

statement that cysts that have the structure of the intestinal wall suggest sequestration from the intestine. This statement is interesting in view of our observations and those of others.

To this last classification, Ayer, in 1906, added: (4) cysts arising from glandular structure of the intestinal wall and (5) cysts of the normally retroperitoneal organs. However, group 4 is at best only a subdivision of Dowd's group 1, and group 5 does not, by its very definition, comprise mesenteric cysts.

Noisi,[3] in 1907, further subdivided Dowd's group 1 into (*a*) cysts formed by sequestration from the bowel during development and (*b*) cysts formed from Meckel's diverticulum when it arises from the concave side of the bowel. To Dowd's group 3, he added cysts arising from

1. Moynihan: Ann. Surg. **26**:1, 1897.
2. Dowd, C. N.: Ann. Surg. **32**:515, 1900.
3. Noisi, F.: Virchows Arch. f. path. Anat. **190**:217, 1907.

retroperitoneal organs, namely, germinal epithelium, ovary, wolffian body and müllerian duct. He considered half of all mesenteric cysts as acquired and placed so-called lymphatic and chylous cysts in this group.

In 1924, Carter [4] proposed another modification of Dowd's classification, as follows: (1) true mesenteric cysts (embryocystomas, enterocystomas, obstructive), (2) dermoid cysts, (3) cystic malignant disease and (4) parasitic cysts.

Higgins and Lloyd,[5] in 1924, proposed this other classification: (1) those of embryonic origin arising from mesodermal remnants incarcerated behind the developing peritoneum and subsequently migrating forward between its layers; (2) those of intestinal origin arising from the bowel during development as diverticula or possibly at times derived from the persistent portion of the vitelline duct.

Aschner [6] (1924), reviewing twenty different cases from the literature, concluded that the enterocystomas described by most writers were due to faulty involution of the omphalomesenteric duct, but, in his opinion, conclusive proof of this theory must await further observations.

CONCLUSIONS

The idea that a portion of an embryonic tissue or organ may become sequestrated and still continue to develop is not new. A group of epithelial cells with its own connective tissue support may become more or less independent for its growth and develop as a cyst the lumen of which is constantly enlarged by the retention of its own secretion and desquamated epithelium. Miller [7] quoted Lewis and Thyng as finding a "regular occurrence of intestinal diverticula in embryos of pig, rabbit and man." However, he arrived at the general agreement that most juxta-intestinal cysts, even when intramesenteric, have their origin in the vitelline duct or Meckel's diverticulum, and was of the opinion that variation in the location of the diverticulum is marked. Hennig [8] suggested that shrinkage of the mesentery of a laterally placed diverticulum might pull it down into the mesentery. Both of the types mentioned would naturally resemble the adjacent bowel remarkably. The gross and microscopic appearance of Miller's case and our own rather definitely place both of them in the group of mesenteric cysts arising from sequestration. It will be noted that in both instances the inner circular layer of muscle was common to both cyst and bowel. If the cyst had been the result of remnants of omphalomesenteric duct, there

4. Carter, R. A.: Surg. Gynec. Obst. **33**:544, 1921.
5. Higgins, T. T., and Lloyd, E. L.: Brit. J. Surg. **12**:95 (July) 1924.
6. Aschner, P. W.: Enterocyst of Ileum, Causing Obstruction, Arch. Surg. **9**:226 (July) 1924.
7. Miller, R. T.: Bull. Johns Hopkins Hosp. **24**:316, 1913.
8. Hennig: Zentralbl. f. Gynäk. **4**:398, 1880.

would have been no necessity for such a close relationship. Both the structure and the arrangement of these cysts point to an enterogenous origin by a process of sequestration during embryonic life. We may therefore state that we are dealing with a cyst at the base of the intestine extending into the mesentery and separating its leaves, and not with a true mesenteric cyst, as it is commonly called. This terminology may be considered similar to that used in calling the extension of a uterine fibroid into the broad ligament a "fibroid of the broad ligament."

The onset of the cystic growth in our case may be definitely dated from before the fourth month of embryonic life, because after the fourth month the portion of the intestine forming the cecum rotates downward to the right side, and in our case an undescended cecum was contained in the volvulus. It therefore follows that the cyst must have been large enough to interfere with the normal development of the cecum at or probably before the fourth month of gestation.

To bear out further the probability that most, if not all, mesenteric cysts with an enterogenous histology are not due to growth of remnants of the vitelline duct, we can add the evidence of such reported cases as those in which the cysts were present in the wall of the intestine and in the lumen of the intestine, as well as those in which they were far removed from the usual site of Meckel's diverticulum, e.g., high up in the duodenum or at the ileocecal valve. Such cysts in the lumen of the intestine have been called enterocysts to differentiate them from mesenteric cysts. One, however, is just as much of a misnomer as the other, for what we actually have is three types of enterogenous cysts: (1) cysts in the wall of the intestine, (2) cysts extending into the mesentery and (3) cysts extending into the lumen of the intestine. As implied before, this classification is entirely analogous to the classification of uterine fibroids into intramural, subserous and submucous. Recent articles on this subject have, by their evidence, all tended toward a similar conclusion, and we feel that our report and suggestions deriving from this case help a good deal toward the definite establishment of the nomenclature proposed.

The importance of accepting this nomenclature as reflecting the actual pathologic condition is well illustrated in previous reports of the surgical difficulties encountered in cases of so-called mesenteric cysts. The following résumé of a recent article [9] serves well to illustrate our point:

A girl, aged 3, was admitted to the hospital with a history of periodic attacks of abdominal pain and vomiting since birth. Her abdomen was big and never varied in size. An exploratory operation was performed two days after admission. When the abdomen was opened, a lobulated cyst, the size of a small football, was found attached to the mesentery of the small bowel, about 45 cm. from the ileo-

9. Wade, R. B., and Steigrad, J.: M. J. Australia **15**:465, 1928.

cecal junction. The small bowel appeared to curve in and around the cyst, *making separation very difficult* (italics ours). Therefore, about 25 cm. of small intestine was resected with the cyst. The patient made an uneventful recovery. The microscopic report suggests that the wall of the cyst and the septum between loculi showed a lymphangiomatous structure with conspicuous blood vessels and strands of involuntary muscle in the connective tissue. No epithelial structures were seen. It was called a cyst of lymphatic origin.

We believe this cyst to have been a greatly dilated enterogenous cyst extending into the mesentery. The enormous distention probably caused a complete flattening of the mucosa of the cyst, such as was caused to some degree in our case, and rupture of the muscle wall of the cyst caused its lobulated appearance. It will be noted that an attempt was made at separation of the cyst from the intestine. This same procedure has been attempted in the other cases reported, without success; a resection was necessary in all. As a matter of fact, because of the pathology with special reference to the histology of the cyst and intestine, a separation should not be attempted, but resection should be undertaken at once. The length of the procedure would thus be lessened and useless and harmful manipulation of the viscera be avoided.

SUMMARY

A case of prenatal volvulus of the small and the large intestine in a full-term female colored child with an undescended large intestine was caused by a mesenteric cyst. The cyst was microscopically enterogenous and contiguous with the overlying intestine. It had a mucosa, an inner circular layer and an outer longitudinal layer of smooth muscle and a serosa. The inner circular layer of the cyst split to encircle the adjacent intestine at the junction of the cyst and the intestine, and the outer longitudinal layer was common to both.

Classification of cysts has changed materially from Moynihan's purely descriptive one to the more recent attempts at an etiologic nomenclature. The histologic structure of juxta-intestinal mesenteric cysts has given rise to the idea of their origin from vitelline duct remnants. Against this theory is the fact that these cysts have been found from duodenum to cecum. Lewis and Thyng found a regular occurrence of intestinal diverticula in embryos of pig, rabbit and man. Therefore, these cysts are probably enterogenous in origin, and since they are found in the wall of the intestine, extending into the mesentery, and extending into the lumen of the intestine, we may consider them to be analogous to the intramural, subserous and submucous fibroids of the uterus.

The cyst caused the volvulus before the fourth month of intra-uterine life, as shown by the presence of an undescended cecum in the volvulus.

As a result of the histologic observations, we believe that in these cases separation of the cyst from the intestine should not be attempted, but a resection should be undertaken at once.

IRREGULARITY IN THE ESTRUAL CYCLE OF THE WHITE RAT FOLLOWING OPERATION ON THE OVARIES*

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It was because of a vital clinical interest in the functional menstrual irregularities in young women and in the hope of gaining some information as to the physiology of menstruation and estrum that this study was attempted. Whether estrum and menstruation represent related and similar phenomena is still a debated question, but there is no reason to suppose that in the essentials they are different. The recurring estrual period of the smaller animals and the menstrual period in the higher animals and that of human beings consist of two phases: one during which the uterus is preparing for the reception of the ovum, and one when the unfertilized ovum, together with the endometrium, are degenerating in preparation for another period. In the animal, the external evidence of this recurring phenomenon is the peculiar sexual behavior of the female and the acceptance of the male. This gave origin to the name estrum or rutting period. It occurs during the preparatory or upbuilding phase. In the higher animals and in the human being, the external evidence of the cyclic phenomenon, the discharge of blood, occurs during the degenerating phase and is called menstruation.

One conspicuous feature of most of the cases of true functional irregularity in young women is an interruption of the usual rhythm of the menstrual cycle. This usually begins to be evident soon after the onset of menstruation. There are long or short periods of menstrual bleeding with varying intervals between. At times, there seems to be an attempt to establish a rhythm; for a few months the periods may become almost regular and normal; then suddenly the rhythm becomes entirely disturbed. In some cases, the long periods of vaginal bleeding are more conspicuous than the long periods of amenorrhea. I have accordingly tried to classify the cases into two groups:[1] those of the metrorrhagic type and those of the amenorrheic type of ovarian dysfunction. A person may revert from one type to the other.

It has been noted clinically that after an operation on the ovaries of a younger woman with resection of a large portion of each ovary,

* Submitted for publication, March 26, 1929.

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1. Drips, Della C., and Ford, Frances A.: Irradiation of Ovaries and Hypohysis in Disturbances of Menstruation, J. A. M. A. **91**:1358 (Nov. 3) 1928.

leaving only a small bit of functioning tissue, or after a severe pelvic infection involving the ovaries, often an irregularity of menstruation develops which simulates functional irregularity. That is, an absolute lack of rhythm develops, so that short or long periods of vaginal bleeding, sometimes difficult to check, may follow short or long periods of amenorrhea.

Often, in both the truly functional and the postoperative or post-infection type of irregularity, by substituting ovarian products it is possible to bring about a simulation of regularity; it has seemed, therefore, that in all these groups there is a deficiency of certain ovarian hormones. Just what factor is necessary for the establishment and continuation of the menstrual rhythm is not, as yet, known.

At operation, in cases of ovarian dysfunction, it has been noted that large cystic ovaries were present, or ovaries filled with cystic follicles; what has been described as a sclerotic capsule may be encountered, and the theory has been that the rhythm has been disturbed because of the inability of the follicles to rupture. Therefore, it would seem that the ovaries remain in one phase of the cycle and the endometrium remains in the corresponding hypertrophic phase, and hence the continued bleeding. Operations on the ovaries, such as stripping off the capsules, puncturing the cystic follicles or resecting portions of them, may bring back the rhythm to the cycle, but often only temporarily.

Believing, then, either that inability of the follicles to rupture or that an insufficient amount of functioning ovarian tissue or both might explain the interruption of the rhythm, an attempt has been made to produce a similar irregularity or lack of rhythm in the white rat. Plastic operations were performed on the ovaries which it was believed would either stop the rupturing of the follicles or reduce the ovarian tissue to a minimum. Then, if arrhythmia was established, it was hoped an insight might be obtained into the mechanism of estrum by a study of the attendant ovarian pathologic changes.

The white rat was chosen because the estrual cycle in this animal had been exhaustively studied by Long and Evans [2] and the various stages of the estrual period as evidenced by vaginal smears were known. Also, the white rat stands operation well, and is resistant to disease.

In order that I might become familiar with the normal estrual cycle in the rat and its associated phenomena, a long time was spent studying the cycles. One hundred and twenty-five female rats were observed for periods varying from four weeks to one and a half years. The date of birth, the date of the opening of the vagina and the date of the first estrum were known in many instances. All the rats were kept from males, since coitus, as has been noted by Long and Evans, always

2. Long, J. A., and Evans, H. M.: The Oestruous Cycle in the Rat and Its Associated Phenomena, Memoirs University of California, 1922.

lengthens the interval between estrual periods. Daily vaginal smears were made for all rats. The typical cornified smear occurred every fourth day. This smear was readily detected grossly because the cheesy material could be easily seen on a glass slide. It was the external evidence of an estrual period.

The smears were best taken at the same time each day, because a few hours' difference sometimes made it seem as if there had been a day more or less between the periods of cornification. Any one who has observed many rats for a long time cannot help being forcibly impressed with the regularity of the cycle. I wish to emphasize this, since from certain available literature it would seem that the cycle was subject to variation due to changes in rations and in living conditions. The rats had the same rations as the other rats in the laboratory: oats, prepared animal biscuits and bread and milk every few days. The number in each cage was limited to five. The rats were of a hardy strain, a mixture of wild and laboratory strains. There were a few litters that seemed to tend to some irregularity, but, in general, the regularity was as predominant as is regularity of menstruation among women. Ordinary illnesses, such as respiratory infections and diseases of the ear, which are common among rats and often severe, apparently had little effect on the regularity of the cycle.

In a few rats with diarrhea and considerable emaciation, the cycles stopped. This usually occurred as soon as emaciation was evident. Only fourteen of the rats died of intercurrent infection, so there was not much opportunity of observing the effect of disease on the cycle. Marked irregularities of the cycle, such as short or long-continued periods of cornification with varying intervals between, were found at necropsy to have occurred in rats with marked pelvic infections, pus being present in the cornua and adhesions being found about the ovaries. These observations were interesting in view of the experimental work. It has been difficult to determine how long the ovarian activity continues in the rat. Rats born in the laboratory were still having regular periods at the age of 19 months. After this, the periods seemed to become more irregular. The average length of life is about 2 years. The vagina opened at seventy days, on the average, and the first estrum occurred at seventy-eight days, on the average. There was some irregularity of the cycle for the first two months. This consisted in longer intervals, usually a multiple of four days between periods of cornification, so that for experimental purposes it was best to use rats about 6 months of age. Estrum was not observed during pregnancy; it was noted several times during lactation. It was possible at times to miss the typical cornified or estrual smear grossly, so that to be absolutely sure of the stage of estrum in vital experiments one had to fix the slides and stain them with hematoxylin and eosin.

My primary interest, as stated, was to try to produce irregularities in the cycle of the rat which might add something to the knowledge of the physiology of the ovaries, and to the understanding of why these irregularities occur in human beings. Healthy female rats, aged about 6 months, were observed for a sufficient period to know they were having normal cycles, and then operations were performed on the ovaries with a view either to stopping the rupture of the follicles or to reducing the healthy ovarian tissue to a minimum or both.

EXPERIMENTAL PROCEDURES

In the first series of rats, both ovaries were exposed and pure carbolic acid was applied to the surface of each, either with the periovarian membrane intact or after it had been stripped. In the second series, one ovary was completely removed and the remaining ovary treated, as in the foregoing procedure. In the third series, a fine needle was run many times through both ovaries in an attempt to rupture all the follicles present and to produce a reaction throughout the ovary. In a few cases, one ovary was removed and the remaining one was needled.

Twenty-eight animals, in all, were operated on. These operations were all done under ether anesthesia and with the most careful aseptic precautions. By the application of carbolic acid to the surface of the ovaries, it was hoped both to reduce the amount of functioning ovarian tissue and to cause enough fibrous adhesions about the ovary to prevent the follicles from rupturing. After the operation, daily vaginal smears were taken and the cycles observed for a long period. A litter mate was kept as a control for comparison of the cycles. It was soon found that the opening of the abdomen and the anesthetic had no effect on the regularity of the cycle, so that the controls were not subjected to this procedure. Finally the rats were killed, the uterus and ovaries were observed grossly and the organs were fixed in Zenker's solution and embedded in paraffin and studied microscopically. Complete serial sections were made of the ovaries. Only one animal died immediately after operation. This rat should not have been included in the series, as it had had a severe respiratory infection, but it had seemed to recover from this and regular cycles were occurring. Some ascites was noted in the abdomen at the time of operation (tables 1 to 3).

RESULTS

Series 1.—There were eleven animals in the first series. In these, both ovaries were treated with carbolic acid with or without stripping off the periovarian membrane. In only three of the animals did any irregularity follow immediately after the operation and continue to death. This was due beyond a doubt to the marked acute reaction to the carbolic acid for at necropsy dense adhesions indicative of severe peritonitis were present all through the pelvis. In these three animals, a respiratory infection with diarrhea developed, and the animals died or were killed within seventy-eight days after operation. Two were in estrum when killed. The ovaries contained some normal follicles and corpora lutea, and there was evidence of the severe inflammatory reaction. In another animal, irregularity developed after two normal

cycles. This consisted of prolonged periods of cornification with longer intervals between, so that the normal rhythm was decidedly disturbed. Finally, a period did not occur for twenty-eight days. At

TABLE 1.—*Results of Experiments in Which Both Ovaries Were Carbolized (Series 1)*

	Irregularity of Estrual Cycle				
Rat	Appearance After Operation, Days	Character	Days After Operation Before Death	Character of Smear on Day of Death	Structures in Ovaries
1*	80	Periods of cornified cells lasting from three to four days; two long intervals	240	Diestrum; no estrum for forty-five days before death	Left ovary: five old corpora lutea and two or three small follicles. Right ovary: five large cysts, four old corpora lutea, no normal follicles
2*	75	Periods of cornified cells lasting from three to four days; two long intervals	240	Dry; epithelial cells only; first stage (Long and Evans)	Few normal mature follicles and early corpora lutea; several follicular cysts
3†	105	Longer intervals between periods; two prolonged periods of cornification	240	Estrum	Few normal structures; right ovary could not be distinguished grossly; microscopic sections not made
4	105	Longer intervals between periods	240	Estrum	Right ovary could not be detected grossly; microscopic sections not made
5	193	Irregular periods with a tendency to prolongation of cornification	193	Diestrum; no estrum for sixty-eight days before death	Left ovary: only corpora lutea (three appeared to be early). Right ovary: few normal follicles and corpora lutea
6	Immediate	Only two estrual periods on the tenth and sixteenth days	38	Diestrum; no estrum for twenty-two days before death	Few apparently normal structures present; much evidence of inflammatory reaction; ovarian tissue infiltrated with lymphocytes
7	Immediate	Three estrual periods at varying intervals	45	Estrum	About the same as in rat 6; normal structures were present but much inflammatory reaction
8	Immediate	No estrum for thirty-eight days; then fair regularity to death	76	Estrum	Normal structures; marked reaction
9	...	After two cycles, prolongation of periods of cornification with longer intervals between	78	Diestrum; no estrum for twenty-eight days before death	Few fairly normal follicles and corpora lutea; both ovaries so small that they could not be identified grossly
10	80	Prolongation of intervals between periods	180	Diestrum; last estrum two days before death	No large or mature follicles in either ovary; few small but apparently healthy corpora lutea (not early)
11	32	After eight cycles one prolonged period of cornification; irregular intervals between	335	Diestrum; last estrum thirty days before death	Left ovary: several mature follicles and several early corpora lutea. Right ovary: two normal mature follicles and two large corpora lutea (not definitely early)

* Ovaries carbolized after periovarian membrane was stripped off both ovaries.
† Ovaries carbolized after periovarian membrane was stripped off right ovary.

necropsy, the left ovary was found to be extremely small and was embedded in a mass of adhesions; it was not possible to be sure grossly of the right ovary. Microscopically, what was left of each ovary contained a few fairly normal appearing follicles and corpora lutea.

The remaining seven animals did not manifest any immediate postoperative irregularity but continued to have normal, regular cycles from 75 to 105 days after operation, after which each developed some irregularity. In at least five, a definite lack of rhythm was present to

TABLE 2.—*Results of Experiments in Which One Ovary Was Removed and the Other Carbolized (Series 2)*

	Irregularity of Estrual Cycle				
Rat	Appearance After Operation, Days	Character	Days After Operation Before Death	Character of Smear on Day of Death	Structures in Ovaries
1	Immediate	Long and short periods of cornification with long and short intervals between	130	Diestrum; last estrum twenty-three days before death	Five old corpora lutea, one cystic corpus luteum, one small follicle, one degenerating follicle; ovary so small that it could not be detected grossly
2	115	Slightly longer intervals between estrums	240	Estrum	Six or seven old corpora lutea, three follicles changing into corpora lutea without rupturing; no other follicles
3	...	After two estrual periods, prolonged periods of cornification first and later occasional skipping of a period	240	Epithelial cells only; first stage (Long and Evans)	No microscopic sections made; ovary lost in embedding; grossly, it was size of a pinpoint
4	Immediate	Increased intervals between periods; slight prolongation of a few periods of cornification	180	Diestrum; last estrum fifteen days before death	No microscopic sections made; ovary lost in process of embedding; grossly, left ovary was buried in mass of adhesions to lower pole of kidney
5	Immediate	One prolonged period of cornified cells; long intervals	73	Diestrum; last estrum occurred twenty-five days before death	No healthy mature follicles or early corpora lutea
6	Immediate	Periods of cornified cells slightly prolonged; slightly irregular intervals between	530	Estrum	Healthy follicles of medium size, two normal mature follicles, many corpora lutea of various ages, definitely early (?)
7	...	Estrual cycle regular	295	Dry but not cornified; first stage	Three follicles, which appeared healthy; nine degenerating corpora lutea, early (?)
8	...	Estrual cycle regular except for one period of three and one of four days of cornified cells	395	Estrum	Eight corpora lutea of various ages; two corpora lutea cysts, two mature follicles
9	40	Skipped periods, but rhythm seemed to be maintained	395	Late estral smear (moist)	Eight corpora lutea, a few of which appeared early; five mature follicles
10	16	After four cycles, occasional prolonged periods of cornification with varying intervals between	395	Diestrum; last estrum five days before death	Mass of follicles, no corpora lutea, three transformed follicles with ova still present
11	53	Some periods skipped; after the tenth month daily cornified smears for twenty-five days	369	Purulent; last cornified smear occurred six days before death	Severe pelvic and abdominal infection, abscesses; impossible to identify the ovary

the day of death. The pathologic change in all these ovaries was marked. The amount of ovarian tissue had been greatly reduced, the ovaries being so small at times that they could not be detected grossly. However, microscopically, a few large or mature follicles and corpora lutea were present in the ovaries of all but two rats (figs. 1 to 4).

Rat 1 did not have an estrum for forty-five days before death, but the smear of rat 10 was positive two days before death. In both these animals, the irregularity began eighty days after operation and continued to death. The cycle was entirely without rhythm in rat 1.

Series 2.—In the second series, there were eleven animals in which one ovary was removed and the other ovary carbolized. It was hoped that by removing one ovary the amount of functioning ovarian tissue might be reduced still more. In four of these animals, the cycle became irregular immediately after operation. Experience with the first series seemed to show that the reaction to the carbolic acid had perhaps been

TABLE 3.—*Results of Experiments in Which Both Ovaries Were Needled (Series 3)*

	Irregularity of Estrual Cycle				
Rat	Appearance After Operation, Days	Character	Days After Operation Before Death	Character of Smear on Day of Death	Structures in Ovaries
1	30	Prolonged periods of cornification with varying intervals between	165	Diestrum; last estrum ten days before death	Right ovary: normal structures present; increase in fibrous tissue; left ovary could not be identified
2	Immediate	A long interval without periods (diarrhea a factor ?)	120	Diestrum; estrum two days before death	A few normal structures in both ovaries; the amount of ovarian tissue was greatly reduced
3*	64	After sixteen cycles, several periods of cornification lasting several days; however, rhythm appeared to be maintained; late long intervals between periods	140	Bloody vaginal smear; fairly recent blood clot in left cornu; last estrum occurred fifteen days before death	Normal structures present
4†	Immediate	Periods of cornification at very irregular intervals	129	Estrum	No microscopic sections made; the ovarian tissue was greatly reduced grossly

* Right ovary entirely removed.

† Left ovary entirely removed.

more marked in these rats, but they all survived this initial period of reaction and were observed for a considerable period; some irregularity continued in all, and was marked in rats 1 and 5. These two had a complete lack of rhythm after operation and the estrual periods seemed to cease entirely, in rat 1, 117 days after operation and in rat 5, 48 days after operation. The animals were killed 130 and 78 days, respectively, after operation, and healthy mature follicles or early corpora lutea were not present in the remaining ovary of either. The remaining ovary of rat 1 was so small that it could not be detected grossly; it was found by cutting serial sections of tissue from the ovarian region (fig. 5). Certainly, in these two animals, a complete lack of estrual rhythm simulating the postoperative irregularities in young women had been produced by reducing the ovarian tissue to a minimum.

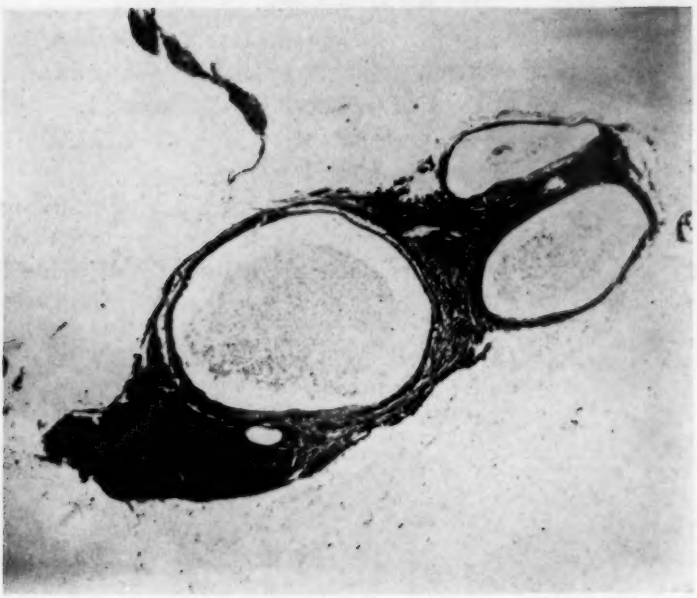

Fig. 1 (rat 1, series 1).—Cross-section through the right ovary of a rat in which both ovaries had been carbolized after the periovarian membrane was stripped off. The ovary shown contained five large cysts and four old corpora lutea. Normal follicles were not present.

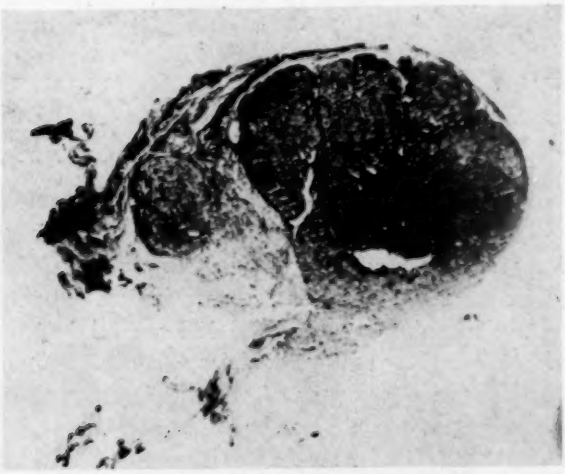

Fig. 2 (rat 1, series 1).—Cross-section through the left ovary of a rat in which both ovaries had been carbolized after the periovarian membrane was stripped off. There were five corpora lutea, none of which appeared to be an early structure, and three very small follicles.

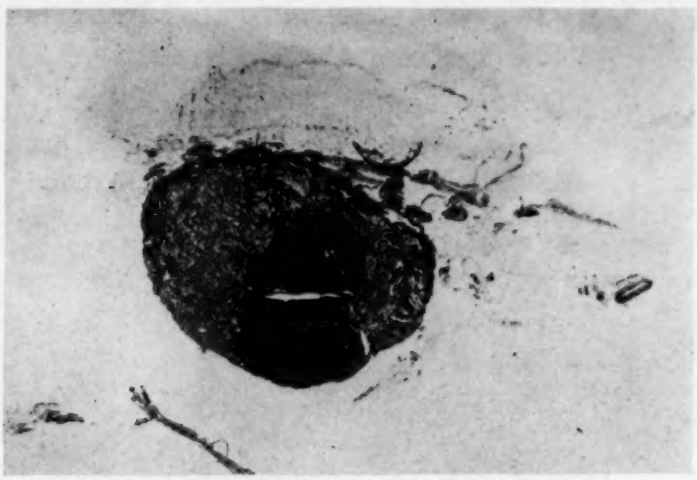

Fig. 3 (rat 10, series 1).—Cross-section through the left ovary of a rat in which both ovaries had been carbolized. This ovary could not be detected grossly. It was found by serial sections. It contained three corpora lutea. Follicles were not present.

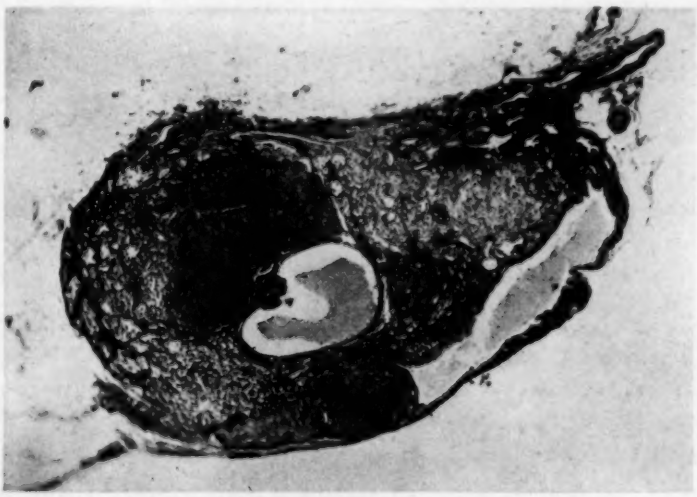

Fig. 4 (rat 10, series 1).—Cross-section through the right ovary of a rat in which both ovaries had been carbolized. There were present several corpora lutea, two cysts and many atretic follicles. Healthy follicles were not present.

The estrual cycle in rat 3 became irregular after two estrual cycles, and sometimes rhythm was entirely lacking. After 240 days, the animal was killed in estrum. There was present grossly a tiny bit of ovarian tissue on the right, too small to measure. It resembled a cyst about the size of a pinpoint. It was lost in the process of embedding. The estrual cycle in rat 2 became irregular after 115 days. This animal was killed 240 days after operation during estrum. The ovary contained seven old corpora lutea and three follicles changing into corpora lutea without rupturing.

Three animals of the second series maintained more regular periods than any of the animals operated on. They were all observed for

Fig. 5 (rat 1, series 2).—Cross-section through the remaining ovary of a rat in which the other ovary had been removed and the remaining one carbolized. The ovary was surrounded by organs from which it could not be separated. It contained five small corpora lutea and one fairly healthy follicle.

thirteen months and all were in a stage of estrum when killed. These in their single remaining ovaries showed the largest number of normal follicles and corpora lutea of any of the animals operated on.

In rat 10, after four regular, normal cycles, the cycles became irregular; definite rhythm was not maintained; occasional prolonged periods of cornified cells with varying intervals between occurred to the day it was killed, thirteen months after operation. The last estrum occurred five days before death. The remaining ovary was made up of a mass of follicles. Corpora lutea were not present. These follicles

were being transformed into corpora lutea without rupture, the ova being still present in the structures (fig. 6).

In rat 11, a late pelvic infection apparently completely upset the rhythm; a prolonged period of cornification lasting twenty-five days occurred shortly before death.

Series 3.—In the third series, in which both the ovaries were needled or one was removed and the other needled, success in reducing the amount of functioning tissue or in preventing the follicles from rupturing

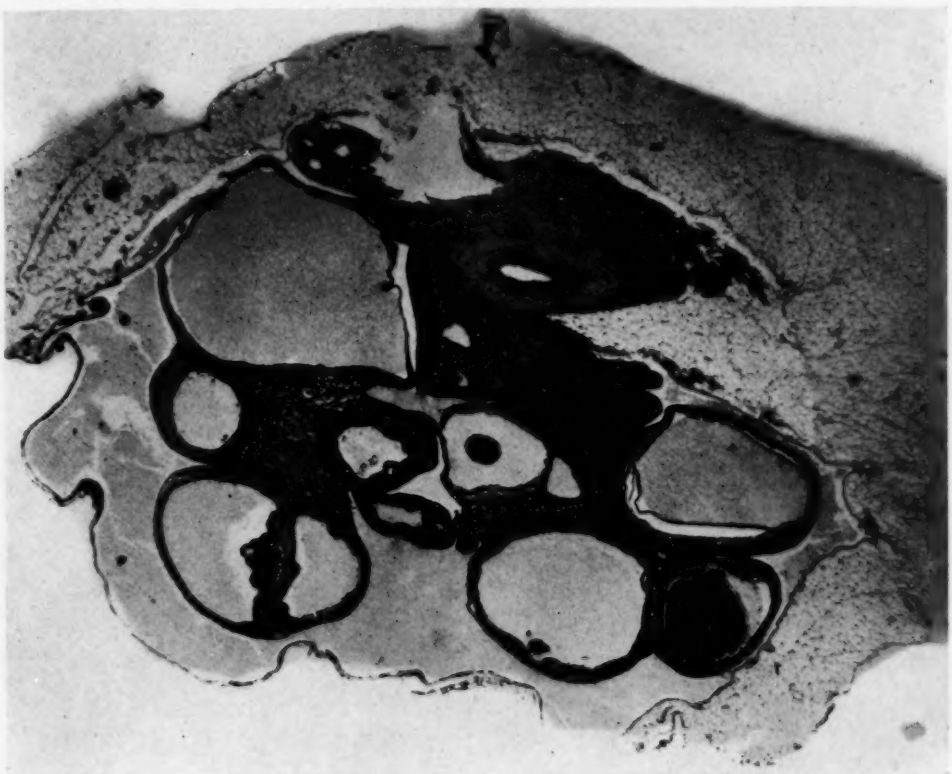

Fig. 6 (rat 10, series 2).—Cross-section through the remaining right ovary of a rat in which the left ovary had been removed and this one carbolized, It is shown surrounded by the distended periovarian membrane, filled with fluid. The ovary itself was a mass of follicles and follicular cysts. Corpora lutea were not present.

was not so complete. An irregularity of the cycle developed in each case, however, and in two cases the irregularity came directly after operation and continued. In two animals (rats 1 and 4), the cycle was entirely without rhythm. The cycle in rat 1 did not become irregular until thirty days after operation, but thereafter prolonged periods of cornification continued to occur with varying intervals between them

until the animal was killed 165 days after operation. The left ovary could not be identified. The right ovary contained a few normal structures. There was a marked increase in fibrous tissue. The cycle in rat 4 became irregular following operation and continued so, the cycle being entirely without rhythm. The animal was killed in estrum, 129 days after operation. The left ovary was very small and was lost.

Naturally, it was difficult to gage just how much destruction of tissue occurs as a result of experimental trauma to the ovaries. As it happened, in the second series of rats each of which had had one ovary entirely removed, there were three rats that had more healthy structures in their remaining ovaries than any animals of the first series, in which

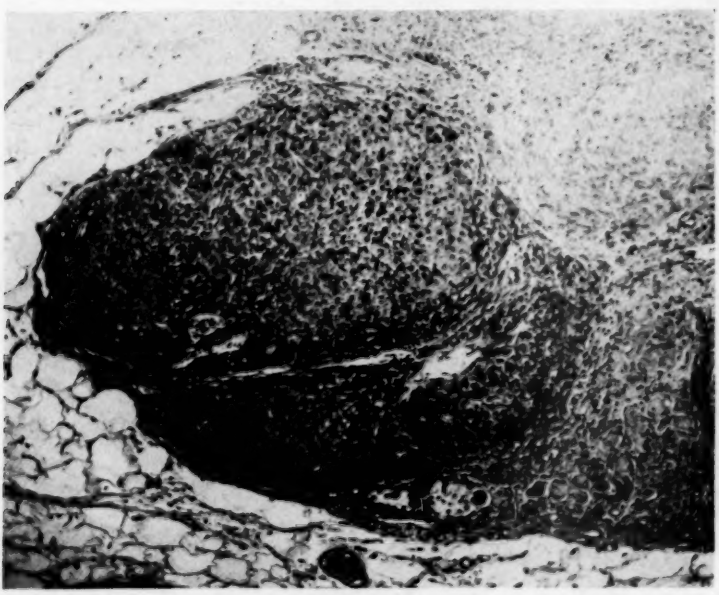

Fig. 7.—A section through two corpora lutea, which was the only remaining ovarian tissue found in a rat that had a number of estrual cycles following double oöphorectomy.

both ovaries were left. In these three animals, the most regular cycles occurred to the date of death, thirteen months after operation.

It seems evident then from these experimental results that in animals in which the smallest amount of functioning ovarian tissue remained, the cycle showed the most irregularity, in some of them occurring entirely without rhythm.

The smallest bit of functioning tissue was obtained entirely by accident. On April 11, 1928, both ovaries were removed from several rats. Vaginal smears were taken daily after the operation as usual and on May 11, a positive smear was obtained from one of these rats. On

May 23, 24 and 26 and June 17, the smears were again positive. The animal was killed on July 2. There was in the region of the right ovary a small piece of tissue which appeared like tissue surrounding a ligature. In the region of the left ovary there was also a tiny bit of tissue; this had a yellowish cast and looked like ovarian tissue. Both these masses of tissue were saved and sectioned serially. The one from the right side revealed only fibrous tissue. The one from the left side showed two corpora lutea so close together that they appeared almost as one (fig. 7). This is the smallest bit of ovarian tissue which I have found would produce estrual periods.

CONCLUSIONS

It is concluded from this study that the ovaries of the rat can be severely traumatized without producing any effect on the estrual rhythm, that the amount of ovarian tissue can be considerably reduced and that the ovaries can be surrounded by adhesions so dense that the follicles apparently cannot rupture and expel their ova, without interfering with the estrual rhythm. But in cases in which the ovarian tissue is greatly reduced, irregularities of the estrual cycle occur, and if the amount of functioning tissue is reduced to a minimum, complete lack of rhythm is exhibited, consisting of short and prolonged periods of cornification with varying intervals between, strikingly similar to the complete irregularity of the menstrual cycle in women after operations on the ovaries. A study of the resulting ovarian pathologic changes after these operative procedures in the animal seemed to prove that one factor in the maintenance of normal estrual rhythm is certainly a sufficient amount of healthy ovarian tissue. It seems that estrum can occur without follicles being present in the remaining ovarian tissue, but in no instance did the cycle continue with neither follicles nor corpora lutea present. Brambell, Parkes and Fielding [3] have stated that the estrual cycle in mice is maintained with ovaries that do not contain follicles or corpora lutea, the ovaries having been treated with roentgen ray when the rats were 3 weeks old.

3. Brambell, F. W. R.; Parkes, A. S., and Fielding, Una: Changes in the Ovary of the Mouse Following Exposure to X-Rays: I. Irradiation at Three Weeks Old, Proc. Roy. Soc., London, ser. B. **101**:29, 1927.

SPONTANEOUS RUPTURE OF THE AORTA*

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Spontaneous rupture of the aorta implies that partial or complete loss in the continuity of the vessel wall takes place without any evidence of extrinsic pathologic changes, trauma or formation of an aneurysm with secondary mural perforation.

The extrinsic causes of penetration of this large vessel are relatively frequent and such penetration must be differentiated from the true type. These include conditions producing erosion of the vessel wall from the external surface or surrounding structures; as tuberculous, inflammatory or malignant changes of the mediastinal or tracheobronchial lymph glands, carcinomatous or ulcerative lesions of the esophagus, destructive conditions of the vertebrae and malignant or inflammatory changes of the lungs.

Trauma in such form as to result in crushing of the thoracic cage occurs most frequently when the direction of the applied force is in the anteroposterior diameter of the chest. Numerous examples are recorded of large objects flying at a high velocity or a crushing between freight trains, etc., having resulted in tears of the large blood vessel. Jaffé and Sternberg [1] recorded the lesion as having occurred in six aviators who had fallen from high altitudes. The undue force exerted on the normal supporting structures of the aorta had resulted in tears in the artery in certain anatomic positions. The sites of predilection for the lesion will be discussed later.

In previous records of this lesion, the gross description of the vessel is usually given in sufficient detail to permit the conclusion that the vessel wall was not normal, but thorough microscopic descriptions are usually lacking. In two of the three cases to be reported, it is to be noted that the gross changes are not sufficient to explain the cause for the laceration, and that on histologic examination the alterations are considerably more marked than one is led to believe from macroscopic examination. Riley [2] reported a spontaneous rip of the thoracic aorta in a boy, aged 16, who had suddenly died while at work. The aorta was the site of a tear 1 cm. long, 2.5 cm. above the cusps on the left

* Submitted for publication, April 3, 1929.

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1. Jaffé, R. H., and Sternberg, H.: Der Fliegertod: Ein Beitrag zur Frage der traumatischen Aortenrupturen, Vrtljschr. f. gerichtl. Med. **58**:3, 1919.

2. Riley, De W. G.: Spontaneous Rips of the Thoracic Aorta with Aneurysm, Atlantic M. J. **27**:743, 1924.

lateral wall, which had ruptured into the pericardial sac; the latter contained about 100 cc. of blood. This was associated with a saccular aneurysm that was directed posteriorly. An anatomic diagnosis of status lymphaticus was made because the thymus weighed 60 Gm. and the mediastinal and abdominal lymph glands were hyperplastic. The other example noted by him was that of a 35 year old hunchback who fell down in a street-car and died in transit to the hospital. It was obtained that the spinal deformity had followed a fall in infancy, and that three months previously the patient had had lobar pneumonia. The autopsy revealed that the aorta was curved sharply to the right. On the convexity there was an aneurysm 4 by 1 cm., a slit 3.7 cm. long on the posterior wall, 1.8 cm. above the aortic ring, and an old slit, 2.5 cm. above the right extremity of the recent tear. In neither of these instances was a microscopic description recorded, but both vessels were undoubtedly the sites of considerable changes, as evidenced by the associated aneurysms in both and an old healed lesion in the latter. What influence the fall had on the hunchback with an already distorted aorta is a subject for theoretical discussion.

Usually the rupture takes place during moderate physical exertion, and is attributed to a concomitant elevation of the blood pressure. Paschkis [3] referred to a white man, 46 years of age, who collapsed while walking and died in four hours. The aorta, 1½ fingerbreadths above the valve, was ruptured longitudinally for a distance of 2.5 cm. The intima and media were penetrated but the adventitia was intact, and the latter was separated from the rest of the wall throughout the ascending and descending portions of the thoracic aorta. There was no perforation into the pericardial sac, but the latter contained a hemorrhagic fluid. Adjacent to the rupture there appeared to be a scar. He stated that microscopic examination of the wall revealed no changes and the Wassermann test of the blood was negative. Oppenheim [4] had a 53 year old patient with subacute glomerulonephritis, who died while on the toilet. Busse [5] reported an instance of death under the same circumstances. Bohnen [6] found a rupture 2 cm. above the aortic cusps and in the arch that occurred during severe labor pains. At the time, severe thoracic pain was complained of. The patient was 26 years of age. The autopsy demonstrated, in addition, fatty and calcific changes of the

3. Paschkis, K.: Ruptur der anscheinend normalen Aorta, Med. Klin. **21**: 1921, 1925.

4. Oppenheim, F.: Gibt es eine Spontanruptur der gesunden Aorta und wie kommt sie zustande? München. med. Wchnschr. **65**:1234, 1918.

5. Busse, O.: Ueber Zerreissungen und traumatische Aneurysmas der Aorta, Virchows Arch. f. path. Anat. **183**:440, 1906.

6. Bohnen, P.: Ueber einen Fall von Aortenruptur unter der Geburt und einen Fall von Septumdefekt, Zentralbl. f. Gynäk. **51**:2398, 1927.

basilar and carotid arteries and severe sclerosis of the ascending aorta. Bohnen here recorded that the elevation of the blood pressure at the height of labor pains may be from 60 to 100 mm. of mercury. The author cited four similar instances, and stated that rupture of the aorta had also occurred during eclamptic convulsions.

The condition can occur without physical exertion. Paschkis [3] quoted Süss in reference to a 48 year old patient whose aorta ruptured while he was lying in bed. The gross and the microscopic appearances of the vessel were regarded as normal.

The relation that trauma has to rupture of the aorta is of tremendous medicolegal importance; for if abnormal changes are present before the injury, the amount of the trauma necessary to produce the lesion can be very slight. In arriving at a judgment as to compensation, therefore, it is necessary that the condition of the artery, gross and microscopic, be taken into consideration. Gallagher [7] wrote on the occurrence of an aortic rupture in a 56 year old white man who was recovering from influenza and, in addition, had clinical evidence of aortitis with moderate dilatation of the heart and a blood pressure of 158 systolic and 106 diastolic. The aortic second sound was accentuated, and over the same area there was a loud systolic and diastolic murmur, and a systolic murmur over the mitral region. The patient died suddenly, and at the autopsy the aorta showed a ragged laceration just above the valves. The intima of the vessel was studded by numerous atheromatous plaques. The heart was surrounded by a layer of blood 2 cm. thick. Maitland [8] noted a tear 1 inch (2.5 cm.) long and ½ inch (1.27 cm.) distal to the site of the common carotid artery in a 49 year old man in whom the aortic second sound was not clear, and who developed evidences of cardiac decompensation following acute appendicitis complicated by deferentitis and funiculitis, and in whom later it was necessary to amputate the right leg because of gangrenous changes. His blood pressure was 160 systolic and 95 diastolic, and the Wassermann reaction of the blood was one plus. The significance of the infectious processes in the patients of Maitland and Gallagher cannot be stated.

Löffler [9] emphasized the underlying factor of nephritis. In both his patients, the aorta was not normal grossly and in the first patient hypertension was present with a reading as high as 224 systolic. In this patient there was a transverse laceration, 4 cm. long, in the ascending aorta, with a rip extending at right angles to it, which was 1 cm. long.

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7. Gallagher, E. T.: Rupture of the Aorta into the Pericardial Sac, U. S. Vet. Bur. M. Bull. **2**:972, 1926.

8. Maitland, C. D.: Spontaneous Rupture of the Aorta, Brit. M. J. **1**:79, 1925.

9. Löffler, W.: Ruptur der Aorta bei chronischer Nephritis, Cor.-Bl. f. schweiz. Aerzte. **48**:185, 1918.

The second patient, a man 43 years of age, had a systolic blood pressure varying from 160 to 180 and an enlarged heart. The aorta, 6 cm. below the ductus Botalli, was torn transversely for a distance of 8 mm. through the intima and media. It is to be noted in these two cases that undoubtedly other factors than nephritis must be taken in consideration.

Coarctation of the aorta with hypertension proximal to the occluded portion is a relatively frequent cause of spontaneous tearing of the aorta.

Nonsyphilitic ulcerations or focal inflammatory changes in any location in the aorta not infrequently occur, with destruction of all layers of the wall, and perforation takes place into the surrounding structures or extends between the layers of the aorta forming a dissecting aneurysm, which may even reenter the vessel at a different point.

That syphilitic mesa-ortitis sometimes is one of the underlying factors was observed by Uhles [10] in a woman 40 years of age, in whom cardiac decompensation was manifested over a period of years and eventually a left hemiplegia. On physical examination, the essential observations were an enlarged heart with a diastolic murmur over the aortic area, and a blood pressure of 248 systolic and 125 diastolic. Though her condition was improving under the administration of digitalis, she died suddenly while walking. The postmortem examination revealed 270 cc. of blood in the pericardial sac, and a left ventricle that was 20 mm. thick. The aorta was studded by numerous fatty and calcified plaques with an indented rupture 5 cm. long in the anterior wall, 1 cm. above the aortic cusps. This tear penetrated the media, but left the adventitia intact, except for a small opening that led into the pericardial sac. The microscopic diagnosis was syphilitic mesa-oritis, slight sclerosis of the renal blood vessels and foci of encephalomalacia in the region of the central ganglions. Gsell [11] called attention to the frequent association of spontaneous rupture of the aorta with small areas of acute and recurring necrosis of the muscle fibers of the media. This necrosis may be syphilitic, but is observed also in cases in which syphilis can be excluded. For the latter instances, he assumed a nonsyphilitic infection or toxic injury of the aortic wall.

In the cases to be reported, it is to be noted that a combination of factors enters into the explanation of each of the spontaneous ruptures of the aorta.

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10. Uhles, B.: Ueber einen Fall von Aortenruptur mit Blutung in die Perikardhöhle, Med. Klin. **20**:49, 1924.

11. Gsell, D.: Necroses der Aortenwand als unabhängige Erkrankung und ihre Beziehung zur spontanen Ruptur der Aorta, Virchows Arch. f. path. Anat. **270**:1, 1928.

REPORT OF CASES

CASE 1.—A colored man, 58 years of age, a laborer, entered the medical service of Dr. Harry Singer complaining of cough, swelling of the feet and shortness of breath over a period of four weeks. His past history revealed that he had been advised by a physician not to work because of some pathologic cardiac condition. He had had pneumonia twice, and at the age of 25 and again at the age of 30 he had had rheumatism. His wife had given birth to two children who were living and well, but she had had three miscarriages. In addition, the patient had had nocturia, being disturbed from three to four times a night for a period of several years. Physical examination revealed a poorly nourished colored man, orthopneic and coughing considerably. The temperature was 99.6 F., the pulse rate 104 and respiratory rate 26. The blood pressure was 198 systolic and 120 diastolic. The pupils did not react to light. In the right lower lobe, posteriorly, there were dry, coarse râles. The apex of the heart was located in the fifth intercostal space in the anterior axillary line, and the valvular sounds were rather rough, but no murmurs were present. The lower extremities were slightly edematous. The urine showed no abnormalities and the Wassermann reaction of the blood was negative. Roentgenologically, it was noted that the left ventricle was enlarged. The condition of the patient improved rather rapidly under the administration of digitalis and rest in bed. On the fourteenth day, he was able to be up and about, but at 10 p. m. he complained of considerable precordial pain, and became restless, noisy and short of breath. He died at 1:30 a. m.

Autopsy revealed a poorly nourished colored man. The abdomen was free from any changes, except that the lower margin of the liver was 1 fingerbreadth below the right costal margin and 3 fingerbreadths below the tip of the xyphoid process. In both pleural cavities there were fibrous bands attached to the mid-portion of the posterior aspect of the lungs extending to the parietal pleura, and the right side of the diaphragm was at the level of the fifth rib and the left side at the level of the sixth.

The heart, with the pericardial sac, and the aortic arch weighed 1,030 Gm. The pericardial sac was enormously distended; the left border was located in the midaxillary line, and the right, 3 cm. to the right of the right sternal border. The sac contained 300 cc. of a hemorrhagic fluid and a blood clot, from 2 to 3 cm. thick, which completely enveloped the heart. The heart was in a state of firm contracture, and on the epicardium was an irregular, round, white area, 2 cm. in diameter, on the anterior aspect of the left ventricle, 3 cm. below the base. The myocardium was firm and a light reddish brown. The diameter of the left ventricle was 10.5 cm. Considerable flattening of the trabeculae near the apex and thickening of the endocardium over the left side of the interventricular septum were present. Several dark red patches were seen in the subendocardium of the anterior wall of the left auricle, the largest measuring 1 cm. in diameter. Similar smaller patches were present in the wall of the right auricle just above the attachment of the middle cusp of the tricuspid valve.

The aorta above the valves measured 82 mm., and there were numerous slightly elevated, irregular, light yellow plaques above the aortic cusps. Three centimeters above the valve was a transverse rupture of the aortic wall, which involved the entire circumference of the vessel. The edges of the tear were smooth, and near the left end of this defect was another tear 3 cm. long, extending in the longitudinal axis of the ascending aorta. This formed a triangular flaplike structure, the tip of which extended upward to within 1 cm. of the innominate artery. The portion of the aorta distal to the laceration was retracted upward for a distance of 2 cm.; thus the wall of the vessel, in this portion, consisted of

adventitia only, which was lined on the inside by blood clot and small, grayish-white tags. In the direction of the valve, the adventitia was completely separated from the other parts of the aorta, and the space between the aorta and the pulmonary artery was filled by dark red blood clots. These surrounded an opening in the adventitia which had a diameter of 20 mm. and led into the pericardial sac. The edges of the opening were indented, and the defect itself was crossed by a fibrous strand. The peripheral part of the ruptured aorta was practically closed by the separated intima, which was pushed as a duplicate fold into the lumen. The

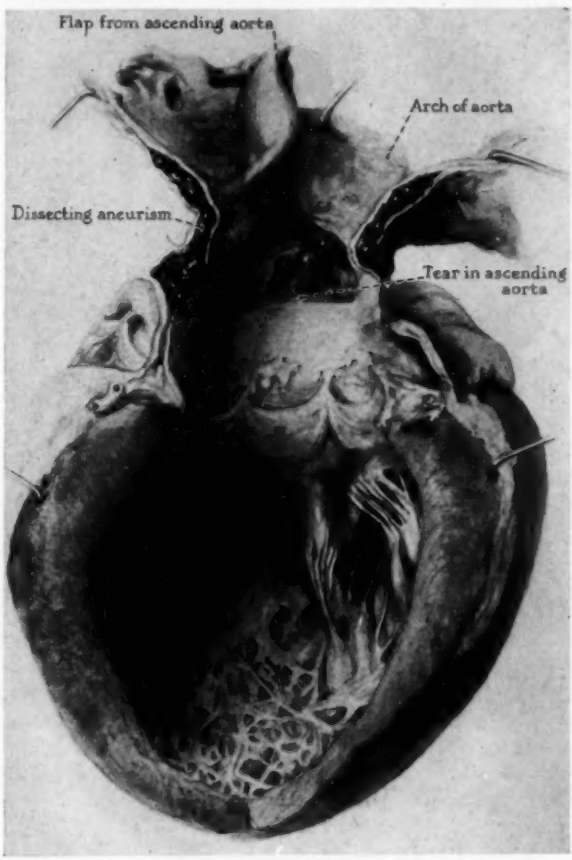

Fig. 1.—A spontaneous tear of the aorta, 3 cm. above the aortic cusps, with only slight atheromatous changes in the supravalvular region.

descending aorta was wide, with a circumference of 60 mm. at the diaphragm and of 42 mm. at its bifurcation. The intima was studded by numerous irregular, linear depressions, which were most abundant near the arch, where there was a moderate number of flat, yellow plaques, which also extended through the aorta and into the larger blood vessels. The descending thoracic portion was the only region in which there was a moderate amount of wrinkling and puckering of the intima.

The liver weighed 1,520 Gm. The surface was reddish brown, and the surfaces made by cutting showed distinct markings and were wet with blood. The gallbladder contained three stones shaped like mulberries, and ranging in diameter up to 8 mm.

The spleen weighed 99 Gm. The surface was wrinkled, and there was an increase in the fibrous elements throughout the substance.

The lungs were crepitant throughout. They were devoid of any changes.

The kidneys together weighed 230 Gm. Their external surfaces were reddish brown and slightly granular, and there were several cortical cysts varying from 2 to 5 mm. in diameter.

Microscopic Examination.—Several sections taken from the edges of the tear in the aorta revealed numerous capillaries extending from the adventitia into the media, which were surrounded by accumulations of lymphocytes and plasma cells. In the media were, also, numerous areas of calcification, and in the intima deposits of lipoid material. Other sections taken from the arch were free from changes.

Sections removed from the left ventricle of the heart showed numerous accumulations of myocytes in nodular arrangement (Aschoff bodies) about the medium-size arteries.

The medium-size arteries of the kidneys, and especially the smaller ones, were considerably sclerosed, resulting in narrowing of their lumen, and there were foci of atrophy and compensatory hypertrophy.

Comment.—The patient presented clinical evidence of cardiac decompensation following an infection of the upper respiratory tract, associated with enlargement of the heart and hypertension secondary to sclerosis of the medium-sized and smaller arteries. His response to the administration of digitalis and to rest was rapid, permitting him to be up and about. Then he suddenly suffered the rupture of the ascending aorta, with perforation into the pericardial sac. The factors predisposing to the lesion were: the disease process in the aorta, the hypertension with marked hypertrophy of the left ventricle, the renewed physical exertion and possibly the administration of digitalis. The gross appearance of the ascending aorta lent the impression that the vessel was the site of atheromatous changes only, but the microscopic examination revealed the presence of syphilis, which was more or less confined to the site of the rupture. This emphasized the importance of examining various regions of the vessel and particularly that near and including the defective portions. However, the possibility of rheumatic aortitis cannot be excluded in view of the work of Pappenheimer and von Glahn,[12] who demonstrated lesions in the aorta associated with acute and chronic rheumatic myocarditis. In these sections of the vessel, the syphilitic changes may have obscured the microscopic pathologic changes. Associated with these changes of syphilitic and possibly rheumatic origin was the presence of considerable amounts of lipoids in the intima with small areas of calcium deposits. These inflammatory and degenerative changes undoubtedly markedly altered the functional capacity of the muscular and elastic tissues of the involved regions and as a result the dilatability of this portion of the aorta was markedly diminished. The added load of a compensating heart, together with the increased muscular power of the left ventricle as the result of treatment with digitalis, and the physical effort of being up and about were sufficient to rupture the already damaged elastic and muscular fibers.

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12. Pappenheimer, A. M., and von Glahn, W. G.: Lesions of the Aorta with Acute Rheumatic Fever and with Chronic Cardiac Disease of Rheumatic Fever, J. M. Research **44**:489, 1923-1924.

CASE 2.—This patient entered the Grant Hospital on the service of Dr. J. E. Siebel on Oct. 5, 1928. She was an Italian woman, married, 41 years of age, who on the day of admission, while eating lunch, complained of severe precordial pain, became short of breath, fainted and was immediately sent to the hospital. Anuria was present for the first twenty-four hours, and she was semicomatose at times during the first day. Her previous history revealed that she had had severe headaches for a few weeks past. However, there had been no previous dyspnea or precordial pain. Her blood pressure on the day following admission was 178 systolic and 134 diastolic. The temperature varied from 98 to 101 F., the pulse rate fluctuated from 82 to 120 during the four days before her death, and the respiratory rate increased from 22 to 36. Roentgen examination of the chest showed marked enlargement of the cardiac area.

The autopsy, for a report of which I am indebted to Dr. S. Brown, revealed an obese, pale white woman, weighing about 190 pounds (86.2 Kg.), with a thick and short neck. In the abdominal cavity there was about 500 cc. of clear, straw-colored fluid and in each pleural cavity 1,000 cc. of a similar fluid. About the apex of the right lung and the base of the left were numerous fibrous adhesions. The pericardial sac was filled with blood and was firmly adherent to the left lung through fibrous adhesions. There were a few scars in the pleura of the lungs. In the right pulmonary apex and in the middle of the left base was a subpleural nodule, 1 cm. in diameter, which was partially calcified and filled by yellowish-white material. The remainder of the lungs was dry.

The heart, with the attached pericardium, and 8 inches (20.32 cm.) of the aorta, weighed 685 Gm. The aorta, externally, appeared dilated, and on being opened revealed a transverse slit in the intima and media, two fingerbreadths above the aortic ring and involved all except 1 cm. of the circumference of the aorta. Extending to the left and posteriorly and opening into this slit was a sac the size of an egg, the wall of which was thin and lined by firm, deep red blood clots. In one of the thinnest places of the wall was an opening of pinhead size leading into the pericardial sac. The entire outpouching was within the pericardial sac. The lining of the aorta, above and below the rupture, was smooth except for a few small fatty plaques. On the inferior convex surface of the transverse aorta were two fatty plaques, each 1.5 cm. in diameter. The coronary orifices and the vessels were patent. Numerous punctiform hemorrhages were present in the subepicardial tissues. The myocardium of the left ventricle averaged 20 mm. in thickness and was pale brown, and the papillary muscles were thickened.

The liver weighed 1,745 Gm. and was soft. The surface made by cutting had distinct acinar markings and was pale brown and mottled yellowish white. The gallbladder contained thick, golden-yellow bile.

The spleen weighed 231 Gm. The capsule was wrinkled and the pulp dark red.

The right kidney weighed 231 Gm., and the left 302 Gm. The capsules stripped easily, leaving a pale, slightly granular surface. The parenchyma was pale and the markings were indistinct.

The suprarenal glands were large and the cortex and medulla were moderately increased.

Microscopic Examination.—In the outer third of the media of the aorta (above the rupture) there were single dilated capillary blood vessels surrounded by small groups of lymphocytes, swollen histiocytes and a few plasma cells. The intima was thickened by large deposits of cholesterol esters and fatty-acid needles located near the media; the fatty changes extended into the media, and there were numerous lipoid granules about the elastic fibers of the media. The adventitia was

thickened and slightly sclerosed, and there were loose accumulations of lymphocytes and plasma cells. The blood had broken into the media, separating the outer from the middle third. Recent hemorrhages were found in the adventitia. Where the capillaries invaded the media, the elastic fibers were spread apart, and in places the continuity was interrupted.

The large plaque near the ductus botalli was composed of hyaline connective tissue with large deposits of lipoids in the deeper parts of the media, which also contained capillaries surrounded by lymphocytes.

In the aorta (below the rupture), the intima and the internal two thirds of the media were separated from the rest of the wall by a large recent hemorrhage, composed of fibrin, platelets, erythrocytes and numerous leukocytes.

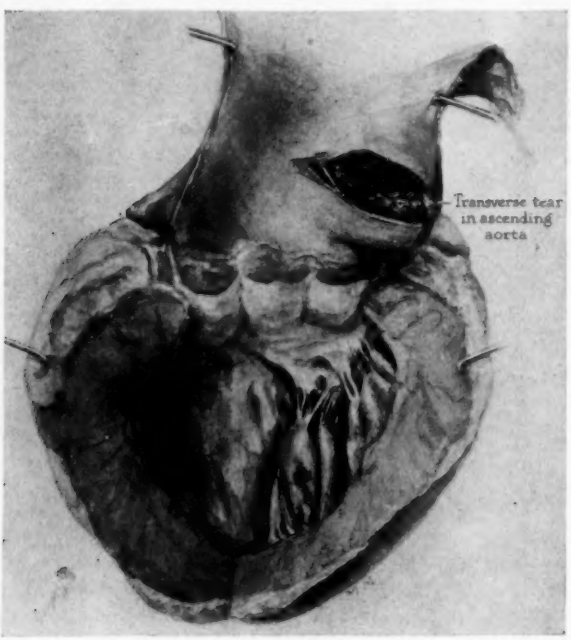

Fig. 2.—An incomplete transverse tear, 1½ fingerbreadths above the aortic cusps, with marked hypertrophy of the myocardium of the left ventricle.

The kidneys showed distinct thickening of the walls of the arterioles and small subcapsular scars in the cortex. Bowman's spaces of the glomeruli were dilated and filled with palely stained and finely granular material. Bowman's capsules were thickened. The muscle fibers of the myocardium were distinctly thicker than normal, and their nuclei had irregular shapes and contained much chromatin. The cross-striations were obscured.

Comment.—In this instance, the lesion occurred, although there evidently were no symptoms referable to any pathologic cardiac or vascular changes and the precordial pain was not so severe as in the first patient and the course following the rupture was more prolonged, owing to the fact that the opening from the aorta into the pericardial sac was considerably smaller, thus causing a more gradual compression of the heart. The pathologic changes in this case are of marked importance in that the gross appearance did not suggest the possibility

of syphilitic changes, but the microscopic alterations were relatively marked, particularly in the region of the rupture. The factor of hypertension again played an important rôle in causing local destruction in the already damaged vessel wall. In addition to the syphilitic process, considerable lipoid degeneration had to be taken into consideration.

Case 3.—A colored man, 56 years of age, entered the medical service of Dr. Sidney Portis, in the Cook County Hospital, on Feb. 7, 1929. The patient said that he had been in good health until the year 1926; then he had become short of breath; this complaint had increased in severity, so that in December, 1928, he was unable to sleep when flat on his back, and his ankles had become edematous. In the three years before his entrance, he had lost 25 pounds (11.3 Kg.) in weight. Thirty years previously he had had a chancre, for which he had not received any antisyphilitic treatment.

Physically, he was well developed and well nourished but was very short of breath. His temperature was 98 F., his pulse rate 102 and his respiratory rate 26 per minute. The blood pressure was 180 systolic and 120 diastolic. The aortic dulness was markedly increased toward the left. The cardiac apex was in the eighth intercostal space in the midaxillary line, and the right border of the heart was 1 inch (2.5 cm.) to the right of the right sternal border. There was a systolic and diastolic murmur over the mitral area. The edge of the liver was palpated 5 fingerbreadths below the right costal margin. Marked edema of the lower extremities was present. The Wassermann test of the blood was negative. The content of urea nitrogen in the blood and the urine was free from any significant changes. During the five days that he was in the hospital before his death, he received 20 drops of tincture of digitalis three times a day and was kept at absolute rest. His pulse, however, became irregular. He was restless and gradually passed into a comatose state and died without any complaint of precordial distress.

The essential observations at autopsy revealed a well developed and well nourished colored man with purplish discoloration of the skin of the head, neck and finger-tips. The veins of the upper thoracic and cervical regions were markedly distended by blood. The lower extremities were edematous. About the right upper and the left lower pulmonary lobes were fibrous adhesions, and in the right pleural cavity was 400 cc. of clear, straw-colored fluid. The pericardial sac extended from the right costochondral junction to the left anterior axillary line.

The heart weighed 600 Gm. Both ventricles were dilated, the left ventricle measuring 10 cm. transversely and 12 cm. longitudinally. The myocardium of the left ventricle was 22 mm. thick and that of the right 6 mm. thick. The heart muscle was rather friable and pale brown-gray. The trabeculae in the left ventricle were markedly flattened. In the coronary arteries were a few slightly elevated, yellowish-white plaques.

The aorta was markedly dilated, having a circumference of 95 mm. in the supravalvular region, 60 mm. at the level of the diaphragm, and 46 mm. at its bifurcation. The intima of the ascending portion was smooth except for a few flat, light yellow plaques, which varied from 3 to 7 mm. in diameter. On its anterior aspect, 20 mm. above the right aortic cusp, was a flat circular depression 5.5 cm. in diameter. At the upper edge of this depression, just below the innominate artery, was a roughly triangular defect in the wall with its apex directed downward, having a base 5 cm. across and a vertical measurement of 4 cm. This defect was surrounded by a smooth and partially undermined edge and its floor was composed of firm, whitish tissue, which gradually merged with the surrounding aortic wall. At the lower angle of this triangular area was an oval opening,

2.5 by 1.5 cm., which led into a semicircular sac having a diameter of 6 cm. and a depth of 3 cm. This sac was located within the pericardial sac and was adherent to the anterior and right lateral wall of the ascending aorta. This cavity was filled by soft, dark red blood clots and its outer surface was gray-brown and covered by thin fibrous tags.

In the arch of the aorta, in the region of the left subclavian and carotid arteries, there was a transverse ring of light yellow plaques, which was from 5 to 7 mm. wide. Between the plaques were fine, irregular, linear depressions.

In the descending aorta, 5 cm. below the opening of the left subclavian artery, there was a circular opening, 5 cm. in diameter, located in the left latero-anterior portion of the wall. This opening led into a large cavity that bulged into the left upper pulmonary lobe. The cavity was 7 cm. deep and 9 cm. longitudinally by 8.5 cm. transversely; it was filled by dark-red blood clots and compressed the left main bronchus, which was filled by thick mucopurulent material. The upper portion of the left upper lobe was airless, but the remaining lung substance was subcrepitant. The lining of the descending aorta was smooth, except for a few small, yellow plaques and linear depressions. There was another irregular opening, near the celiac artery, located on the anterior aspect of the aorta, which was of triangular shape, having a base 20 mm. in width and measuring 30 mm. longitudinally. This opening extended upward for a distance of 1 cm. beyond the junction of the thoracic and abdominal portions. This defect contained soft, deep red-gray blood clots, which separated the intima and the media from the adventitia. Two centimeters below this opening was a longitudinal slit 30 mm. long, located 10 mm. to the left of the superior mesenteric artery and extending downward to the region of the renal arteries. Near these tears were numerous flat, yellow-white plaques from 3 to 5 mm. in diameter.

The kidneys together weighed 300 Gm., and contained numerous cysts from 5 to 15 mm. in diameter that replaced much of the renal parenchyma. The capsules were slightly adherent to a dark purplish-gray surface that was studded by pink-gray and gray-white nodular elevations from 1 to 3 mm. in diameter. The cortex was 5 mm. wide and gray-brown, and the markings were obscure. Microscopically, there were marked hyalinization and lipoid infiltrations of the arteriolar walls. The majority of the glomeruli were well preserved, but a few were obliterated by hyaline material.

Microscopic Examination.—The flat, circular, depressed area in the ascending portion of the aorta revealed typical syphilitic changes and, in addition, the adventitia was irregularly separated from the media. The latter was markedly altered in that the normal stratification of the muscle fibers was lacking, and had been partially replaced by irregular round areas of myxomatous-like tissue. The nuclei in these portions assumed a whorl-like arrangement in the peripheral zones, whereas in the central areas their arrangement was irregular and they varied in size and shape in that they were elongated, round, triangular or stellate in outline. This type of tissue extended toward and formed the inner wall of this portion of the ascending aorta and there was no intimal lining present in this area.

Comment.—In this patient, the clinical manifestations of gradual cardiac decompensation extended over a period of about three years. There was a history of primary syphilitic infection thirty years previously and, in addition, marked hypertension with cardiac hypertrophy most likely secondary to the arteriolosclerosis of the kidneys. In spite of the fact that there were a healed lesion and two recent ruptures in the aorta, the patient presented no clinical indications of these pathologic conditions.

SUMMARY

In these three instances of spontaneous rupture of the aorta, it is to be noted that although the vessel may be free from extensive gross inflammatory or degenerative changes, nevertheless, as microscopic examination demonstrates, considerable destruction of the vessel wall may have occurred in places, and it is at these points that the vascular wall has a tendency to tear. However, other conditions must also be taken into consideration in that frequently the aorta is the site of extensive degenerative and inflammatory changes. Nevertheless, spontaneous rips do not occur frequently. Sudden increase in the blood pressure as the result of renewed physical exertion, excessive exertion and possibly the administration of digitalis play important rôles in the causation of tears in diseased aortas.

From the foregoing correlation of gross and microscopic alterations in the aortic wall, it is obvious that careful microscopic examination is necessary in all instances, especially, of the edge of the rupture. Legally, the latter observation should be taken into consideration when the lesions occur following various amounts of trauma.

As is so frequently the occurrence in syphilitic aortitis, the Wassermann reaction of the blood was negative in two of the three instances reported, and in the third there was no examination of the blood by either the Kahn or the Wassermann method.

Most frequently, the rupture of the aorta occurs either 1½ finger-breadths above the aortic cusps or in the region of the ductus botalli, whether the condition has occurred spontaneously or following trauma. Various reasons for this choice of site have been tendered, but that of Rindfleisch [13] is most generally accepted, namely: first, there is a fibrous union between the ascending aorta and the pulmonary artery which serves as a fixed point, and second, there is an obliteration of the ductus arteriosus with fixation of the aortic arch. The portions of the aorta surrounding these regions are relatively movable and therefore the vessel tears at the two points of fixation.

That healing can occur following a spontaneous rip of the aorta is exemplified in the last reported instance, which microscopically shows a healing process characteristic of a wounded or lacerated vessel wall.

Although this lesion occurs most frequently at the points of fixation of the thoracic aorta, the last case presented two tears below the diaphragm. However, the local destruction in these areas was marked and the blood pressure was high.

13. Rindfleisch, E.: Zur Enstehung und Heilung des Aneurysma Dissecans Aortae, Virchows Arch. f. path. Anat. **131**:174, 1893.

CONCLUSIONS

1. Spontaneous rupture of the aorta occurred in three instances 1½ fingerbreadths above the aortic cusps, and in one of these there were two tears of the vessel below the level of the diaphragm.

2. The gross changes at the site of such a rupture are frequently inadequate to explain the tears, but localized microscopic alterations of a syphilitic and degenerative nature are marked.

3. Medicolegally, microscopic examination at the site of the rupture is important.

4. A combination of contributing factors must be taken into consideration, which include the local destructive process and the conditions that increase the blood pressure. The latter may be on an arteriosclerotic, nephritic, functional or therapeutic basis.

THE STRUCTURAL CHANGES OF THE LIVER IN PERNICIOUS ANEMIA

A CONTRAST BETWEEN RELAPSE AND REMISSION*

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Medical science has taken a great stride with the contribution in 1926 by Minot and Murphy on the treatment for pernicious anemia with the ingestion of large amounts of liver or kidney. This treatment promptly, rapidly and with regularity benefits strikingly the health of most patients with this disease. The number of red blood cells returns to normal and is maintained at that level if proper amounts of liver or a potent substitute are taken. Cohn, with Minot and Murphy and their associates,[1] showed that an extract of liver produces the same results, and that the active principle is probably a nitrogenous base which acts to promote the growth of the primitive cells which crowd the bone-marrow in relapse. Consequently, a method to relieve the patient with pernicious anemia is now known, and something has been learned of the nature of the substance essential for recovery. A further advance has been made by Castle,[2] who demonstrated that whereas the ingestion of 200 Gm. of beefsteak has no effect on pernicious anemia, the anemia may be promptly alleviated by the daily feeding of 200 Gm. of beefsteak predigested in a normal stomach. This indicates that normal gastric juice, although by itself incapable of such action, is essential for the elaboration of this curative substance from meat, and suggests that the achylia gastrica which is always present in this disease may be an etiologic factor. The primary etiology of pernicious anemia, however, remains obscure, and investigators are still in the dark with regard to the forces which bring about the various pathologic alterations in the body.

One may speculate on the probable substance or substances essential for the maintenance of the normal composition of the blood. Whether the changes occurring in pernicious anemia are due to a failure of the elaboration of a hypothetic substance or substances, or whether the anemia and other bodily changes are due primarily to constitutional or

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* Submitted for publication, April 24, 1929.

* From the Thorndike Memorial Laboratory of the Boston City Hospital.

1. Minot, G. R.; Cohn, E. J.; Murphy, W. P., and Lawson, H. A.: Treatment of Pernicious Anemia with Liver Extract, Am. J. M. Sc. **175**:599, 1928.

2. Castle, W. B.: Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia, J. Clin. Investigation **6**:2, 1928.

acquired factors, remains to be established. The various links in the chain necessary for a complete understanding of the nature of pernicious anemia will be obtained only by careful study of the disease from its inception through the various stages of relapse, remission and return to an apparently normal condition. Among the factors that some investigators have thought important in the etiology of the disease is the state of the liver; thus, a review of this topic seemed desirable. The pathologic histology of the liver in twenty patients not treated with liver, and in five treated with liver, who died from intercurrent disease while in partial or complete remission, is the subject of this paper.

It is conceded usually that Combe [3] in 1822 recorded the first case that was presumably one of pernicious anemia. His record of the liver is that it was light brown. Addison,[4] neither in his original article (1849) nor in his monograph in 1855,[5] made any statement as to the pathologic changes of the liver. In 1857, Samuel Wilkes [6] reviewed the postmortem observations of a group of cases and was impressed by the presence of an increased amount of fat in some, but not in all, of the livers.

The first important contribution to the pathologic condition of the liver in pernicious anemia was made in 1877 by Quincke,[7] who noted that there was an increased iron content in this organ, to which condition he gave the name siderosis. The significance of this, however, was masked in his mind by the knowledge that the patient had been treated with iron, and he thought that the ingested iron was the cause of the siderosis. William Hunter,[8] in 1889, was the first to stress the importance of the iron-containing pigment in the liver and other tissues. He accumulated data to show that there was a considerable increase in the iron content of the liver in pernicious anemia over that normally present and an amount in excess of that occurring in most other anemias.

Textbooks on general pathology state little about the liver in pernicious anemia. They usually record that fatty degeneration may be found in some cases, but that siderosis of the liver is a characteristic

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3. Combe, J. S.: History of a Case of Anemia, Tr. Med.-Chir. Soc. Edinburgh, May, 1822.

4. Addison, T.: Anemia: Diseases of the Suprarenal Capsules, London M. Gaz. **43**:517 (March) 1849.

5. Addison, T.: Idiopathic Anemia: On the Constitutional and Local Effects of Disease of the Suprarenal Capsules, London, S. Highley, 1855.

6. Wilkes, Samuel: Cases of Idiopathic Fatty Degeneration, Guy's Hosp. Rep. **3**:203, 1857.

7. Quincke, I.: Weitere Beobachtungen über pernicioser Anamie, Deutsches Arch. f. klin. Med. **20**:1, 1877.

8. Hunter, William: On the Pathology of Blood Destruction within the Liver, Tr. Med.-Chir. Soc. Edinburgh, April 1887; Pernicious Anemia, London, Charles Griffin & Company, 1901.

feature and that foci of focal necrosis may occur. In addition to this, one often finds quoted the observation of Meyer and Heineke,[9] in 1907, that accumulations of myelocytes and erythroblastic cells may be found in the liver. Other authorities, except Piney, added nothing further in regard to blood formation in the liver in pernicious anemia. In 1925, Piney[10] wrote that "in all cases of pernicious anemia it is possible to find intravascular islets of pure megaloblastic tissue in the hepatic capillaries, and their arrangement is identical with that seen in the embryo." There is but little reference in the literature to the morphology of the Kupffer cells in pernicious anemia. Moffitt[11] stated that hypertrophy of these cells occurs.

THE LIVER OF PATIENTS DYING IN SEVERE RELAPSE FROM PERNICIOUS ANEMIA

The observations here recorded were made on twenty patients with pernicious anemia who were not given liver therapy and who died with profound anemia.[12] The material studied consisted of sections of liver from each patient, cut from paraffin blocks and stained with eosin and methylene blue (methylthionine chloride, U. S. P.). A general survey of the tissue was made with the low power microscope, while the finer details were studied with the oil immersion lens. The entire field of the tissue was covered during the examination. The examination was conducted with the following subjects particularly in mind: the size of the Kupffer cells and whether they contained pigment and phagocytosed red blood cells; the amount of siderosis of the liver cells; the presence of erythropoiesis; the occurrence of megaloblasts in the sinusoids and the amount of fatty degeneration, focal necrosis and periportal infiltration.

At the time of death the red blood cells in all except two cases numbered less than 1,000,000 per cubic millimeter; in two cases the count was about 1,500,000 per cubic millimeter.

Marked enlargement of the Kupffer cells was found in each of the twenty cases. The increase in size was due both to an abundance of cytoplasm and particularly to a swelling of the nucleus, so that the cells bulged well out into the lumen of the capillaries. This enlargement was not limited to scattered cells or groups of cells, but was found to be characteristic of all the Kupffer cells and was most apparent in those

9. Meyer, E., and Heineke, A.: Ueber Blutbildung bei schweren Anaemien und Leukaemien, Deutsches Arch. f. klin. Med. **88**:435, 1907.

10. Piney, A.: Some Morphological Factors Governing the Incidence of Pernicious Anemia, Proc. Roy. Soc. Med. **18**:5, 1925.

11. Moffitt, H. C.: Studies in Pernicious Anemia, Am. J. M. Sc. **148**:817, 1914.

12. These cases appear in the hospital record prior to 1926, and, therefore, before the introduction of liver therapy.

cells which had been cut through the central longitudinal plane rather than the periphery. Phagocytosis of red blood cells was present to a moderate degree and was recognized by the presence of whole or disintegrating cells within the protoplasm. The majority of the cells, and principally those at the outer two thirds of the lobule, contained a yellowish-brown pigment.

Not infrequently one end of a Kupffer cell was seen to lie free in a sinusoid while the other end appeared still to be attached to the reticu-

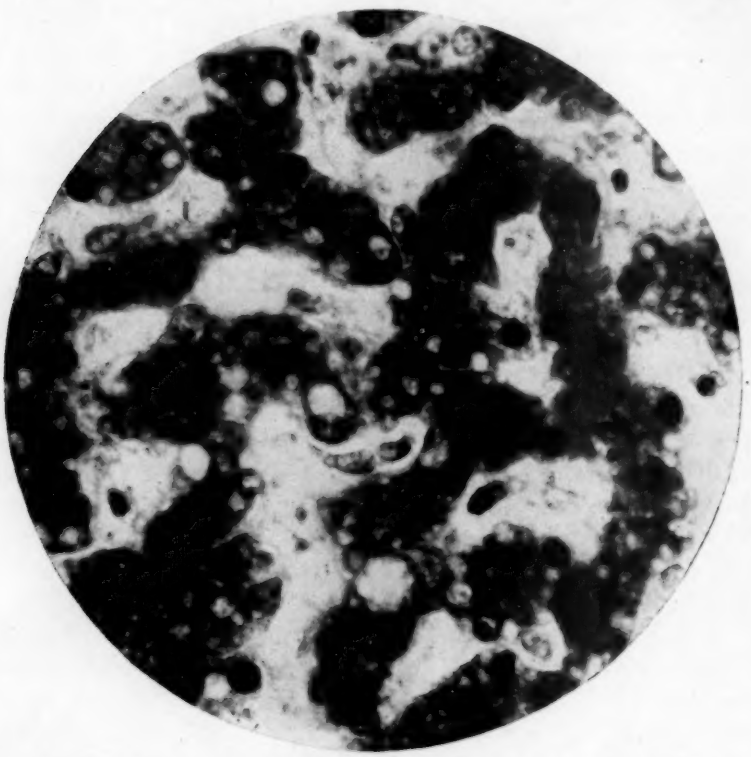

Fig. 1.—The liver in pernicious anemia during a severe relapse; ×750. The pronounced hypertrophy of the Kupffer cells should be noted. Slight fatty degeneration of the liver cells is present.

lum. Such cells apparently were in the process of desquamation. This was made all the more apparent by a study of the cells in the sinusoids, in which there were large numbers of phagocytes. Here they appeared as a single nucleated, round or oval mass of pink-staining protoplasm. There extended from some of the phagocytes a finger-like pseudopod, while others were stretched out as a long slender mass within the capillary. Cells of this sort were all laden with yellow-brown granules of hemosiderin, and with whole and disintegrating red blood cells.

A yellowish or yellowish-brown pigment, evidently hemosiderin, was also found distributed about the periphery of the lobules of the liver and principally in the parenchymatous cells. It was most densely concentrated on the side of the cell adjacent to the bile canaliculi.

In order especially to compare the state of the Kupffer cells in other conditions with those in pernicious anemia, sections of liver were studied from subjects who died from various infectious processes. These were selected in no way and represented routine autopsy material. Included were miliary tuberculosis, chronic bronchitis, tonsillitis, acute peritonitis and subacute endocarditis. In addition, sections of liver from a case of aplastic anemia and from two cases of myelophthisic anemia were studied. In all these cases, the patients had died of a terminal pneumonia. In these livers an occasional hypertrophied Kupffer cell was seen, but for the most part the cells were small and slender. A varying number of desquamated and phagocytic cells in the sinusoids and slight phagocytosis of red blood cells were noted. This reaction, however, was a response of the "reticulo-endothelial system" to infection, and the hypertrophy of the Kupffer cells was certainly slight in comparison to the marked general hypertrophy which occurs in pernicious anemia, although the desquamation of the Kupffer cells and phagocytosis was about equivalent.

In spite of critical examination of the centrally and peripherally placed sinusoids, the space between the parenchyma of the liver and the reticulum of the sinusoids, and the periportal connective tissue, no signs of erythropoiesis were observed in any of the sections from the twenty cases.

It must be borne in mind that in fixed tissues stained with eosin and methylene blue, it is difficult to differentiate the various mononuclear cells. In seventeen of the twenty cases, a comparatively large cell was present in the sinusoids with a moderate amount of blue-staining protoplasm that contained a large round nucleus. The latter was surrounded by a definite basophilic membrane which enclosed a moderate amount of chromatin with a "spoke-wheel" type of arrangement, giving it a reticular appearance; this differentiated it from the monocyte and its larger size from the plasma cell. Such cells seemed to be megaloblasts and did not occur in clumps but only appeared free in the sinusoids. No islets of erythroblastic cells were found such as occur in the liver with extramedullary blood formation.

Fatty degeneration of varying degrees was seen in seven of the cases studied, but the process was never extensive. In seven cases, foci of necrosis were observed, while four showed a slight degree of chronic passive congestion. Fatty degeneration and focal necrosis, however, are not specific features of pernicious anemia as similar changes occur in many other conditions.

Periportal infiltration of lymphocytes and plasma cells with an occasional polymorphonuclear eosinophil were found in seven cases. This condition probably is not of any great significance, but should not be confused with myeloid metaplasia.

THE LIVER OF PATIENTS TREATED WITH LIVER WHO DIED FROM INTERCURRENT DISEASE DURING REMISSION

Several sections of liver were studied from each of five patients who died while in a stage of remission of pernicious anemia produced by liver therapy. The sections were prepared and inspected in the same manner as those from the former group. The salient facts pertinent to the state of the liver regarding these five cases of typical pernicious anemia are recorded below.

CASE 1.—A white man, aged 57, had a red blood count of 655,000 per cubic millimeter and bronchopneumonia at the time of entry to the hospital. Raw liver pulp derived from 250 Gm. of liver was given that day. On the subsequent days until death the patient was fed liver pulp from about 550 Gm. of liver. On the sixth day, the reticulocytes had risen from 0.4 to 18 per cent. Despite a transfusion of blood and symptomatic therapy the pneumonia became more extensive, and on the eighth day, at which time the reticulocytes amounted to 23 per cent, the patient died.

CASE 2.—A white woman, aged 60, first entered the hospital three years before death, with typical pernicious anemia. She was put on an adequate liver diet, and in due time her blood returned to essentially normal. A year before death she decided to reduce her weekly ration of liver to an amount derived from three quarters of a pound. A month before death severe diarrhea developed, and at this time she stopped taking liver. Acute bronchitis and acute cystitis were present when she entered the hospital for the last time. The hemoglobin content was 26 per cent, and the red blood cells numbered 992,000 per cubic millimeter. The reticulocytes numbered 0.8 per cent. She was given daily doses of liver extract no. 343 derived from 400 Gm. of liver. On the ninth day, the reticulocytes had risen to 17 per cent. Pneumonia developed, and the patient died on the eleventh day after the doses of liver extract were commenced.

CASE 3.—A white woman, aged 58, entered the hospital with profound anemia. She was put on a liver diet, and the blood showed prompt improvement. Five months later she was brought back to the hospital in a dying condition, suffering from lobar pneumonia of which she died two days later. The day before death the red blood cells numbered 3,700,000 per cubic millimeter and the hemoglobin content was 70 per cent.

CASE 4.—A white man, aged 57, entered the hospital with a red blood cell count of 1,600,000 per cubic millimeter; the hemoglobin content was 35 per cent. The daily administration of the pulp from 300 Gm. of raw liver was followed by a reticulocyte response of 19 per cent on the seventh day and a rapid rise in the concentration of the red blood corpuscles. He maintained an adequate liver diet at home with evidence that the number of red blood cells became normal. Thirteen months later, he was brought to the hospital in a dying condition, at which time the blood appeared normal; he died the following day from a widespread phlebitis involving the iliac veins, vena cavae and mesenteric veins.

CASE 5.—A man, aged 65, had had a partial prostatectomy eight years before the present entry. One and a half years before death, it was necessary to remove more of the prostate because of progressive obstruction, and he was found to have some urinary infection. Evidence of malignancy was not obtained from the examination of the tissue. It was learned at this time that for the past six months he had some numbness of the hands, and he said that he had "much dyspepsia" all his life. Studies revealed that he had symptoms and signs typical of pernicious anemia. The red blood cells numbered 2,400,000 per cubic millimeter, and the hemoglobin content was 60 per cent. He was put on a diet of liver extract no. 343, and

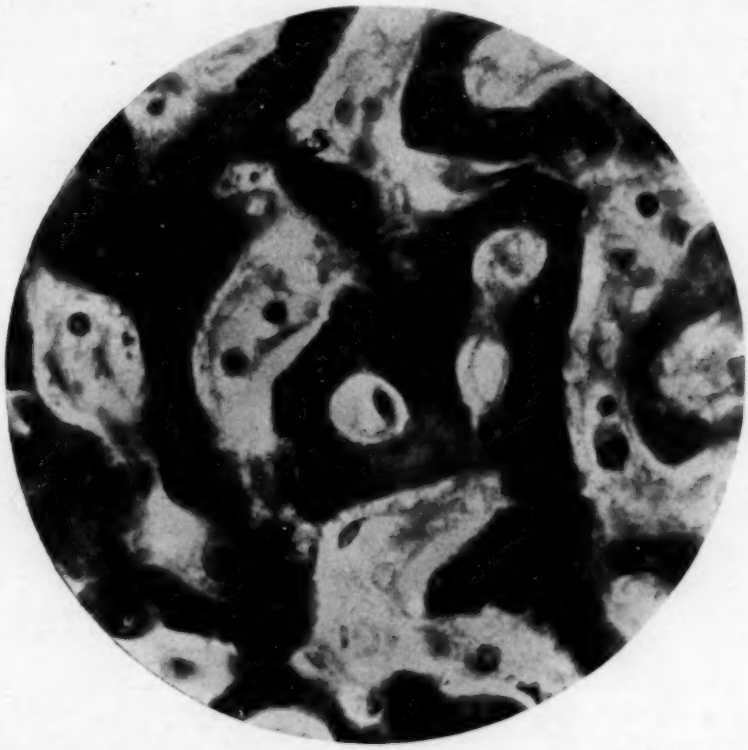

Fig. 2.—The liver in pernicious anemia during a remission. The Kupffer cells appear normal and are short and slender.

within two months the red blood cells amounted to 5,500,000 per cubic millimeter, and the hemoglobin content was 95 per cent. The red blood cells remained at a normal level until two months before death when they numbered 4,000,000 per cubic millimeter. Three weeks before his death from lobar pneumonia, the red blood cells numbered 4,500,000 per cubic millimeter. At autopsy, a carcinoma of the prostate with invasion of local tissues was found.

These cases, therefore, represent different stages and degrees of remission of pernicious anemia at the time of death. In two cases the remission had just commenced. In one patient, who was treated five

months, either the red blood cells had fallen rapidly before death owing to infection, or the patient had taken insufficient liver and had thus not had a complete remission. She was, however, in a state of at least moderate remission. The two other patients died when their blood was essentially normal.

COMMENT

The most striking distinction between the livers of the patients treated with liver and those not so treated was the difference in the size of the Kupffer cells. These cells were much larger in those patients who had not received liver than in any of those who had received liver. In the two patients showing a beginning remission, a moderate number of Kupffer's cells containing pigment was enlarged, whereas those not containing pigment appeared of normal size, except for an occasional cell that bulged into the capillary. In the patients with essentially normal blood at the time of death, the difference in the size of the Kupffer cells was more striking, for most of the cells were short and slender while only an occasional pigment-containing cell or a rare pigment-free cell appeared enlarged. The speed with which the Kupffer cells return to normal size after treatment with liver is suggested by the first two cases, since death occurred within the first eleven days of remission. This observation is of interest in connection with Peabody's [13] studies on the bone-marrow obtained by puncture during life. With the onset of remission he found a decrease in the number of megaloblasts, a cell supposedly arising from the "reticulo-endothelial cell" of the bone-marrow and increasing numbers of normoblasts. Some idea of the time required for the development of hypertrophy of the Kupffer cells can be gained, perhaps, from the study made of the following case.

CASE 6.—A man, in the sixth decade of life, in October, 1925, had a remission of pernicious anemia produced by liver therapy, following which the erythrocyte count remained between 4,500,000 and 5,900,000 per cubic millimeter for two years. On Oct. 11, 1927, the red blood cells numbered 5,000,000 per cubic millimeter, and the hemoglobin content was 80 per cent. Increasing symptoms and signs of a pyelonephritis caused the patient to take practically no liver after about Sept. 1, 1927. His health failed rapidly, and the number of red blood cells fell to 2,200,000 per cubic millimeter four days before his death on Nov. 12, 1927. Autopsy showed very small kidneys with chronic nephritis and pyelonephritis as the chief cause of death.

This case, therefore, is one in which relapse occurred during the month prior to death. Examination of the liver showed marked generalized hypertrophy of the Kupffer cells similar to that found in the twenty untreated patients.

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13. Peabody, F. W.: The Pathology of the Bone Marrow in Pernicious Anemia, Am. J. Path. **3**:179, 1927.

If hypertrophy of the Kupffer cells can be interpreted as indicative of increased activity, the observations given are of interest in connection with the ideas of Jungmann,[14] Muller[15] and others that the entire "reticulo-endothelial system" may be hyperactive in pernicious anemia.

Phagocytosis of red blood cells and desquamation of Kupffer's cells in the sinuses of the liver occur in pernicious anemia. The degree of this activity, however, is not in excess of that occurring in the liver in patients dying of an infectious disease, or a severe type of anemia other than pernicious anemia. It also is no greater during relapse than during remission in pernicious anemia. Phagocytic activity of the Kupffer cells may be a terminal event. This is suggested because of Peabody's[16] observations that phagocytosis in the bone-marrow is more evident at autopsy than in material obtained by biopsy.

Siderosis of the liver was found in both patients treated with liver and in those treated by other measures. The chief difference was one of degree. In the group not treated with liver, the pigment was found in the outer two thirds of the lobule, whereas, in the livers of the two patients who died when their blood appeared normal, the pigmentation was limited to the outer one third. This suggests that some of the pigment had been utilized in the manufacture of red blood cells, and that which remained represented the storage of pigment which had been formed in excess during relapse.

The question of blood formation in the liver in pernicious anemia is of much interest. Piney[17] stated that in pernicious anemia the liver is the only focus of megaloblast production, and he did not consider that this takes place in the bone-marrow. He concluded that the disease can occur only in persons who have a remnant of the megaloblastic tissue from fetal life in the liver. If this were the case, such tissue should be found during remission as well as during relapse in pernicious anemia. This observation of Piney has not been confirmed in this study. In 1905, Gulland and Goodall[18] examined sections of liver from seventeen cases of pernicious anemia. In eight of these they found "giant cells indistinguishable from those of the bone marrow, and the presence

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14. Jungmann, P.: Ueber die Wirkungsweise der Leberdiat bei der perniziosen Anämie, Klin. Wchnschr. **7**:441, 1928.

15. Muller, G. L.: The Influence of Liver and Meat Diets on the Bone Marrow and the Regeneration of Red Blood Cells and Hemoglobin, Am. J. Physiol. **82**:269, 1927.

16. Peabody, F. W., and Broun, G. O.: Phagocytosis of Erythrocytes in the Bone Marrow with Special Reference to Pernicious Anemia, Am. J. Path. **1**:169, 1925. Peabody (footnote 13).

17. Piney, A.: Recent Advances in Haematology, Philadelphia, P. Blakiston's Son & Company, 1928; footnote 10.

18. Gulland, G. L., and Goodall, A.: Pernicious Anemia: A Histological Study of Seventeen Cases, J. Path. & Bact. **10**:125, 1905.

of large numbers of red cells, often nucleated, in the liver sinusoids." This suggested to them that in some cases parts of the liver may revert to its fetal function of blood formation. Meyer and Heineke [9] believed that blood formation occurred in the liver in some cases of pernicious anemia. They described the presence of mononuclear eosinophilic cells as well as a few large, protoplasm-rich, mononuclear cells, which they considered were probably neutrophilic myelocytes. Normoblasts were not found. That blood formation in pernicious anemia occurs elsewhere than in the bone-marrow is doubted by other observers. Schridde,[19] among other investigators, considered Meyer and Heineke's conclusions incorrectly drawn. Warthin [20] found no evidence of red blood cell formation in the lymphatic or hemolymphatic glands, but did not report on the liver. He believed that the presence of nucleated red cells in the sinuses could be explained by their presence in the circulating blood. The evidence from previous studies of blood formation in the liver in pernicious anemia, therefore, is not convincing. The observations recorded in this paper also give no support to such an idea, and as suggested by other investigators, it appears that the presence of megaloblasts in the liver of pernicious anemia is merely the result of their presence in the circulating blood.

SUMMARY

A contrast study was made of the histology of the livers from twenty patients with pernicious anemia not treated with liver who died during relapse, and from five patients treated with liver who died from intercurrent disease while the anemia was in partial or complete remission.

The livers from the twenty patients who died during relapse showed the following:

1. Pronounced general hyperatrophy of the Kupffer cells was noted.

2. Desquamation of Kupffer's cells and phagocytosis of red blood cells were obvious, but were not more excessive than in other severe types of anemia or in infectious diseases.

3. Siderosis was marked in the liver cells and moderate in the Kupffer cells.

4. There was fatty degeneration in seven of the cases; necrosis and periportal infiltration with lymphocytes and plasma cells were present in four of these cases and also in three other cases.

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19. Schridde, H.: Ueber Regeneration des Blutes unter Normalen und Krankhaften Verhaltnissen, Centralbl. f. allg. Path. u. path. Anat. **14**:865, 1908.

20. Warthin, A. S.: Pathology of Pernicious Anemia, with Special Reference to Changes Occurring in the Hemolymph Glands, Am. J. M. Sc. **124**:674, 1902.

The livers from the five patients who died in remission showed the following:

1. The Kupffer cells were of normal size, except for a relative few, which contained pigment. There was indirect evidence that this return to normal occurred within the first ten days of remission.

2. The desquamation of Kupffer's cells and the phagocytosis of red blood cells were equivalent in degree to that found during relapse.

3. Siderosis equivalent in degree to that present during a relapse was noted in cases of early remission. In the two patients whose blood appeared normal at death a slight degree of siderosis was present.

In contrast to Piney's observations, blood formation in the liver was not found in any of the twenty-five patients. Megaloblasts occurred free in the sinusoids of the liver in the patients who died during a relapse.

HISTOLOGIC CHANGES IN THE SPLEEN IN EARLY CONGENITAL SYPHILIS

WITH SPECIAL REFERENCE TO THE ORIGIN OF ANEMIA IN THIS DISEASE *

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MINOT, N. D.

The spleen in congenital syphilis has been the subject of considerable discussion throughout the literature, relatively little of which has concerned histologic change. In an exhaustive review on the pathologic anatomy of congenital syphilis presented before the German Pathological Society in 1928, Schneider [1] emphasized that changes in the spleen vary considerably, since the causes of its enlargement are composite, and more an indirect than a direct result of the syphilitic infection. Schneider observed that these nonsyphilitic changes include passive congestion, destruction and formation of blood and degenerative change. The more specific changes are represented by increase and thickening of reticulum, deposit of blood pigment or lipoid, vascular lesions of infiltrative or proliferative type, gummas and perisplenitis. Lubarsch,[2] according to Schneider, recognized three distinct types of splenic enlargement, based on histologic appearance: (1) passive congestion only, (2) proliferation of the reticulum and thickening of the trabeculae and (3) marked increase in size of malpighian corpuscles.

Considerable attention has also been given to the occurrence of severe anemias, leukemoid changes or both, with congenital syphilis. Hirschfeld [3] pointed out the similarity of these conditions to von Jaksch's disease (anemia pseudoleukemica or pseudoperniciosa infantum). Histologic changes in the spleen in the latter disease are usually characterized by myeloid metaplasia and pulp hyperplasia according to Naegeli [4]

* Submitted for publication, May 17, 1929.

* From the Department of Pathology, University of Minnesota, and the Northwest Clinic, Minot, N. D.

1. Schneider, P.: Ueber die Organveränderungen bei der angeborenen Frühsyphilis, Verhandl. d. deutsch. path. Gesellsch. **23**:177, 1928.

2. Henke, Friedrich; and Lubarsch, Otto: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1927, vol. 1; cited by Schneider.

3. Hirschfeld, H., in Die Krankheiten des Blutes und der Blutbildenden Organe (Enzyklopaedie der klinische Medizin), Berlin, Julius Springer, 1925, vol. 1, p. 152.

4. Naegeli, O., in Die Krankheiten des Blutes und der Blutbildender. Organe (Enzyklopaedie der klinische Medizin), Berlin, Julius Springer, 1925, vol. 1, p. 9.

and Eppinger.[5] Schridde[6] observed that the same changes are often present in the spleen in congenital syphilis. Warthin[7] studied three instances of early congenital syphilis, showing leukemoid blood pictures, and was able to make certain that these cases were not leukemic, by virtue of marked increase of stroma and disappearance of the follicles in the spleen, changes which he considered characteristic of congenital syphilis.

Various theories have been discussed regarding the pathogenesis of anemias in congenital syphilis. Frank[8] divided these anemias into two groups, the one mild without other prominent characteristics, the second severe and accompanied by visceral changes, particularly splenic enlargement. Frank correlated decreasing hemoglobin and red blood cell values with increasing size of the spleen and liver, and implied that the spleen is of etiologic importance. Samberger,[9] however, in discussing the origin of jaundice and anemia, did not mention the spleen as a causative factor, but held the belief that the jaundice was due partly to therapeutic mercury, and partly to a syphilitic disease of the liver. French and Turner[10] reported a case of considerable interest in this regard, the important observations in which may be repeated briefly: A boy, aged 5 years, had had anemia since he was 9 months of age. The spleen was definitely enlarged. The Wassermann reaction was repeatedly positive. The hemoglobin content was 20 per cent; red blood cells, 1,900,000, and white blood cells, 21,000. The clinical diagnosis was: anemia pseudoleukemia infantum (von Jaksch's). Long continued antisyphilitic therapy produced no benefit. Following splenectomy, without further medication, the hemoglobin content rose to 85 per cent, and apparent cure was effected.

In a recent histologic study[11] of seventy spleens from patients with various diseases, particular attention was given to four, three of which were from definite cases of congenital syphilis, and the fourth probably so. Changes of an unusual character were seen in these spleens, and in

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5. Eppinger, H.: Die Hepato-Lienalen Erkrankungen, Berlin, Julius Springer, 1920.

6. Schridde, H., in Aschoff, L.: Pathologische Anatomie, Jena, Gustav Fischer, 1923.

7. Warthin, A. S.: Congenital Syphilis Simulating Leukemia and Splenic Anemia (Banti's Disease), Internat. Clin. **4**:60, 1910.

8. Frank, M.: Zur Klinik der Anämie kongenital luetischer Säuglinge, Monatschr. f. Kinderh. **31**:470, 1926.

9. Samberger: Pathogenese der syphilitischen Anämie und des syphilitischen Ikterus, Arch. f. Dermat. u. Syph. **67**:89, 1903.

10. French, H., and Turner, D.: Case of Splenic Anemia Treated by Splenectomy, Proc. Roy. Soc. Med. (clinical section) **7**:77, 1913.

11. Unpublished thesis submitted to the faculty of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1928.

the following paragraphs these will be described, in each case preceded by a brief clinical and gross pathologic abstract.

CHARACTERISTIC OBSERVATIONS

CASE 1.—An infant boy, aged 2½ months, had respiratory difficulty at the age of 2 months. There was a moderate degree of jaundice. The liver and spleen were large. The abdominal veins were dilated. The hemoglobin content was 50 per cent; erythrocytes, 2,520,000; leukocytes, 22,000, and lymphocytes, 75 per cent. There were frequent normoblasts in blood smears, often with multiple nuclear buds. The serum bilirubin was increased (indirect van den Bergh reaction). The Wassermann reaction was positive. (The Wassermann reaction of the mother was positive also.) The weight of the spleen at necropsy was 39 Gm.

The spleen was fixed by the injection of Helly's fluid (technic described by Watson [12]). The sections were stained with hematoxylin and eosin, and Wright's [13] technic was employed for the tissue. Sections were also stained for hemosiderin, the ferricyanides and ferrocyanides of potassium with hydrochloric acid being used, and they were counterstained with hematoxylin and eosin.

The splenic sinuses were prominent, usually wide and congested; their structure was well preserved. Numerous cells were present in the sinuses, among which macrophages were frequent. Normoblasts were present in considerable number both in the sinuses and in the remaining pulp spaces. These were best recognized in the preparation stained with Wright's technic. Frequent lymphocytes and occasional polymorphonuclear leukocytes were seen. There was no evidence of myeloid metaplasia. The large free phagocytes, as well as the sinus endothelial cells, contained both red blood cells and hemosiderin more or less uniformly. Both normoblasts and mature erythrocytes were phagocytosed. The reticular cells of the pulp contained relatively small amounts of hemosiderin, and phagocytosis of red blood cells was not observed except in sinus cells. Moderate proliferation of the reticular cells of the pulp was noted.

CASE 2.—An infant boy, aged 2½ months, took feedings poorly from birth. The symptoms included vomiting, diarrhea and fever. There was a history of general paresis in the father. Observations in the blood were first recorded shortly after an extensive accidental burn: the hemoglobin content was 44 per cent; erythrocytes, 2,890,000, and leukocytes, 72,000. Frequent immature myeloid cells were noted (leukoblasts, promyelocytes, myelocytes). There were many normoblasts. Anisocytosis, poikilocytosis, polychromasia and hypochromasia were observed. Four days following the burn the leukocytes numbered 16,000, with occasional myelocytes. The hemoglobin content was 35 per cent; erythrocytes, 2,000,000. At necropsy the organs showed no evidence of leukemia. Bilateral bronchopneumonia was present. The spleen weighed 45 Gm. There was no evidence of disease of the liver or pancreas. The epiphyses were not examined. The Levaditi stains gave negative results.

The spleen was fixed in Helly's fluid. Paraffin sections were cut at 5 microns, and stained with hematoxylin and eosin, with Wright's stain and for hemosiderin. The sinuses were prominent and fairly wide, and contained large numbers of erythrophages. There was moderate congestion of the pulp with some diffuse proliferation of the reticular cells. Many normoblasts were seen, often with mul-

12. Watson, C. J.: Histologic Variations in Diffuse Splenic Fibroses, Folia haemat., to be published.

13. Wright, J. H.: Histogenesis of the Blood Platelets, J. Morphol **21**:263, 1910.

tiple nuclear buds both in the sinus lumina and in the pulp spaces. Again, these were best recognized in the Wright stained sections. There was marked hemosiderosis, limited almost exclusively to the sinus macrophages. The sinus endothelial cells were also phagocytic and contained both hemosiderin and red blood cells. The latter often contained nucleated red blood cells or erythrocytes. There was no evidence of myeloid metaplasia. The lymphocytes were increased, and occasional polymorphonuclear leukocytes were observed.

Fixation by injection of Helly's fluid. Camera lucida drawing × approximately 300 (Wright's stain). Marked erythrophagocytosis, congestion of sinuses and increase of lymphocytes. Normoblasts are difficult to recognize in the absence of color, but usually have a wider and less deeply staining cytoplasmic rim.

Congenital syphilis could only be suspected in the foregoing instance. Unfortunately, it was not possible to obtain blood from the mother for a Wassermann test. The appearance of the spleen was almost identical with that in the preceding case. The anemia undoubtedly existed prior

to the severe burn, which, however, was probably the cause of the leukemoid blood picture.

CASE 3.—An infant boy, aged 3 weeks, had a distended abdomen, a large spleen and a palpable liver. There was extreme pallor. The hemoglobin content was 24 per cent; leukocytes, 31,000, and lymphocytes, 80 per cent. The Wassermann reaction was positive. Necropsy revealed syphilitic epiphyses and intralobular cirrhosis of the liver; the spleen weighed 45 Gm. Levaditi stains were positive on various tissues.

The spleen was fixed in a diluted solution of formaldehyde U.S.P. (1:10). Paraffin sections were cut at 7 microns and stained with hematoxylin and eosin, and for hemosiderin. There was moderate congestion of the pulp spaces. The sinuses were prominent, and contained numerous macrophages, as well as lymphocytes, and red blood cells. The large phagocytes contained both erythrocytes and large amounts of hemosiderin. Little was present elsewhere. Normoblasts were frequently observed, both free and in phagocytes. There was moderate proliferation of the reticular cells of the pulp.

CASE 4.—An infant girl, aged 8 weeks, had a papular eruption over the skin, rhagades about the mouth and splenomegaly. Results of examinations of the blood were not recorded. There was temporary improvement after syphilitic therapy.

Necropsy revealed syphilitic osteochondritis and interstitial pancreatitis. The spleen weighed 76 Gm.

The spleen was fixed in a diluted solution of formaldehyde U.S.P. (1:10). Paraffin sections were cut at 7 microns and stained with hematoxylin and eosin, and for hemosiderin.

There was moderate diffuse proliferation of the reticular cells of the pulp. The sinuses were prominent and contained frequent clumps of free cells, including lymphocytes, red blood cells and macrophages. The latter contained both erythrocytes and hemosiderin. Free sinus endothelial cells were also noted. Normoblasts were of frequent occurrence both in the pulp spaces and in the lumina of the sinuses. Hemosiderin was not increased to the extent observed in the three previous instances, although it was present in considerable amount, largely in phagocytes, and to a lesser extent in the pulp spaces.

COMMENT

Although destruction of the blood has been mentioned in the literature as one of the nonsyphilitic changes occurring in the spleen in congenital syphilis, I have not found any description of such marked erythrophagocytosis and hemosiderosis as were observed in the instances reported here. No emphasis has been placed on the occurrence of such changes, nor on their relationship to the severe anemias which are commonly present in congenital syphilis.

The histologic appearance varied but slightly in each of the four spleens described. Numerous macrophages were characteristic, containing both nucleated and mature red blood cells and large amounts of hemosiderin. The phagocytes were almost wholly in the sinuses; attached sinus endothelial cells were also phagocytic. Normoblasts were of frequent occurrence. Evidence was lacking to prove that these were of local origin, and other signs of myeloid metaplasia were absent.

In three of the foregoing instances severe anemias were prominent during life; the characteristics of the blood were not recorded in the fourth. In one of the three patients with anemia, syphilis was not proved to be present although it was strongly suggested. In both instances in which the blood picture was studied, the anemia was of a definitely regenerative type, while in one bilirubinemia was present, and the van den Bergh reaction was indirect. These observations, together with the histologic changes in the spleens as described, constitute evidence that the anemias were hemolytic, and imply that the spleen plays an important rôle in their origin.

CONCLUSION

Extensive destruction of the blood may occur in the spleen in congenital syphilis, and is probably an important factor in the production of anemia. Marked erythrophagocytosis and hemosiderosis is observed as evidence of this destruction. The macrophages are largely of sinus endothelial origin, and fixed sinus endothelial cells are also phagocytic.

THE EFFECT OF ALUMINUM ON MAMMALIAN BLOOD AND TISSUES*

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There is comparatively little to be found in the literature concerning the effects of alum on the mammalian organism, when administered either in large doses or in small doses for long periods. We have therefore undertaken a series of experiments to secure information concerning the toxic effects of aluminum, especially in the form of alum (sodium aluminum sulphate). Two methods of attack were used. In the first, aluminum compounds were injected intravenously, and the effects on the blood cells, on the formation of antibodies and on the tissues were noted. These experiments demonstrated that markedly toxic effects resulted when the aluminum ion was put directly in contact with body tissues. To learn whether aluminum administered by mouth can be absorbed sufficiently to produce similar effects, aluminum compounds were fed in small doses over an extended period of time, and finally large single doses were fed at one time. When effects followed ingestion of the aluminum compounds similar to those caused by direct injection, the conclusion seemed warranted that the aluminum ion is able to pass through the alimentary tract and is then able to do damage to the tissues.

It has been contended that aluminum, as it is commonly eaten in the largest amounts, that is, in the form of food prepared with alum baking powder, is in an insoluble form which resists absorption and passes on through the alimentary tract as inert material. Evidence, however, has been brought to light showing that this may not be altogether the case. Steel,[1] in 1911, showed that aluminum in alum baking powders was not rendered wholly insoluble in the baking process and that it was found in the blood of dogs that ate biscuits made with the powder. Kahn[2] also showed that aluminum was absorbed into the blood stream after ingestion of aluminized biscuits. Much was eliminated in the urine and feces, but a considerable amount was distributed in the various tissues of the body. Aluminum was found by

* Submitted for publication, April 16, 1929.

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1. Steel, M.: Am. J. Physiol. **28**:94, 1911.
2. Kahn, Max: Biochem. Bull. **1**:235, 1911-1912.

Balls [3] in the blood of men fed aluminized biscuits. Evidence was submitted by Myers and Killian [4] that from 2 to 20 per cent of the aluminum compounds ingested in baking powder residues was found in soluble form and a smaller proportion in solution in the gastric contents of eighteen subjects. Somewhat similar observations were made on the solubility of aluminum in the duodenal contents of four subjects.

The French investigators Schaeffer, Fontés, LeBreton, Oberling and Thivolle [5] recently found that aluminum phosphate, as it is found in some baking powders, is soluble both in vitro and in vivo in the hydrochloric acid of the gastric juice. Furthermore, it is not reprecipitated in the duodenum by the alkaline pancreatic juice when the chyme is neutralized. Bile prevents this (precipitation) in an as yet undetermined manner.

Mull, Morrison and Myers,[6] using the aurin reaction of Hammett and Sottery,[7] reported finding less than 0.2 mg. aluminum per hundred cubic centimeters in the blood of thirteen hospital patients with miscellaneous diseases and in pig's blood. Recently Myers, Mull and Morrison [8] reported the aluminum content of rat liver, per hundred grams, to be: 0.130 mg. in control rats; 0.161 mg. in rats fed aluminum; 0.063 mg. in rats fed an aluminum-free diet, and 8.2 mg. in rats receiving intraperitoneal injections of aluminum. They found the aluminum content of dog liver per hundred grams, to be 0.150 mg. in control dogs and 0.266 mg. in dogs receiving aluminum. In the autopsy material from man they found the following amounts of aluminum per hundred grams of tissue: in the heart, 0.225 mg.; in the brain, 0.203 mg.; in the liver, 0.074 mg, and in the gallbladder with bile, 0.069 mg. From their data, they concluded [9] that traces of aluminum are present in the tissues normally and that the amount is slightly increased on a diet containing considerable aluminum. The growth curves of animals receiving aluminum, however, compare well with those of the controls, the only difference being that the rats fed aluminum showed a slightly greater initial growth. They further concluded [10] that when aluminum compounds are administred orally to dogs, the absorption of the aluminum is slight.

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3. Balls, A. K.: Dissertation, Columbia University, New York.
4. Myers, V. C., and Killian, J. A.: J. Biol. Chem. **78**:591, 1928.
5. Schaeffer, G.; Fontés, G.; LeBreton, E.; Oberling, C., and Thivolle, L.: Bull. Soc. d'hyg. aliment. **16**:1 and 49, 1928.
6. Mull, J. W.; Morrison, D. B., and Myers, V. C.: Proc. Soc. Exper. Biol. & Med. **27**:476, 1927; J. Biol. Chem. **78**:595, 1928.
7. Hammett, L., and Sottery, C. T.: J. Am. Chem. Soc. **47**:142, 1925.
8. Myers, V. C.; Mull, J. W., and Morrison, D. B.: J. Biol. Chem. **78**:595, 1928.
9. Myers, V. C., and Mull, J. W.: J. Biol. Chem. **78**:605, 1928.
10. Myers, V. C., and Morrison, D. B.: J. Biol. Chem., **78**:615, 1928.

There have been numerous claims that aluminum is not absorbed into the blood stream following oral ingestion, such as the report by Taylor.[11] In a recent study, McCollum, Rask and Becker,[12] with the use of a spectroscopic method for determining aluminum, were unable to demonstrate that aluminum is a constituent of either plant or animal matter, and stated that compounds of this element are not absorbed out of the stomach or intestinal tract when present in the diet. This is not in agreement with the results of Mull, Morrison and Myers and others and can scarcely be accepted until repeated and confirmed.

EFFECTS OF INTRAVENOUS INJECTIONS OF ALUMINUM

Rabbits were used in all the experiments. The effects of aluminum on the number of red and white blood corpuscles, on the relative proportions of the different leukocytes, on the fragility or the resistance of the red cells to hemolysis with saponin and hypotonic salt, on the percentage of hemoglobin, on the body weight and on the histology of the various tissues, as well as the clinical symptoms, were noted.

The investigations in this part, dealing with intravenous injections of aluminum compounds, were divided into two types of experimentation: One dealt with the effects following intravenous injection of small daily doses of different aluminum compounds over an extended period of time. The other dealt with the effects following intravenous injection of a single large dose or a few large doses, in order that we might determine the amount of sodium aluminum sulphate that can be tolerated at one time.

TECHNIC

The red cell count and the total and differential leukocyte counts were made in the usual manner in a Levy counting chamber, before any injections were given and at frequent intervals thereafter. These counts were made before the rabbits were fed their daily ration. Two counts were made in every case reported in this paper and the average recorded. No numbers were accepted that varied more than from 300,000 to 500,000 erythrocytes or 1,000 leukocytes. The percentage of hemoglobin was determined by the Sahli method, and the fragility of the corpuscles was studied by determining the degree of hemolysis with saponin and hypotonic salt solutions.

The hemolytic methods used were those described by Bigland,[13] with modifications. For example, a series of six tubes was set up, containing the following amounts of 0.8 per cent sodium chloride: 1.4, 1.5, 1.6, 1.7, 1.8 and 1.9 cc. Then 1 cc. of a 1 per cent solution of sheep's blood made in saline solution was added to each tube. And, lastly, the following amounts of a 0.01 per cent saponin saline

11. Taylor, A. E.: Alum in Foods, Bull. 103, U. S. Dept. of Agric., 1914.

12. McCollum, E. V.; Rask, O. S., and Becker, J. E.: J. Biol. Chem. **77**:753, 1928.

13. Bigland, A. D.: Quart. J. Med. **7**:369, 1914.

solution were added: 0.6, 0.5, 0.4, 0.3, 0.2 and 0.1 cc., making a total of 3 cc. in each tube. Each tube was shaken well and allowed to stand at 37.5 C. for two hours and then over night at room temperature. The following day, the amount of hemolysis was read by noting the last tube in which complete hemolysis had occurred. By comparing, in this manner, the number of cubic centimeters of a standard saponin solution required to hemolyze completely a definite amount of blood of a rabbit before treatment, with the amount required after treatment, it was possible to determine whether the fragility of the blood cells was increased or decreased. It was found that the weaker (1 per cent) solution gave more clearcut readings than did a stronger (5 per cent) solution, and still the absolute values obtained in the two cases were identical.

The determination of the fragility of the red cells by means of the hypotonic salt solution was similar in process. A series of nine tubes was set up containing the following amounts of physiologic solution of sodium chloride: 1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8 and 2 cc. To each was added 1 cc. of a 1 per cent solution of whole blood made with saline solution, and then distilled water sufficient to make a volume of 3 cc. The resulting percentage of saline, which was just sufficient to produce complete hemolysis, could be easily calculated and was reported accordingly.

At first, an attempt was made to determine the hemolysis of blood cells washed free from serum, but the excessive bleeding that was necessary to secure adequate amounts for this determination had deleterious effects on the rabbits and greatly complicated the results due to the aluminum solutions. Hence this test was eliminated. The few preliminary experiments performed, however, showed that washed blood cells of normal rabbits are slightly less resistant to hemolysis by saponin than are the blood cells when mixed with their normal serum, a result which confirms the work of M'Neil.[14] There seemed to be no difference in hemolysis with hypotonic salt solution between washed and unwashed cells.

INTRAVENOUS INJECTIONS OF SMALL DAILY DOSES

Rabbits were each given a daily intravenous injection of from 5 to 10 cc. of an aluminum solution containing an amount of aluminum which would be comparable with the amount found by Kahn in the blood stream of dogs that had been fed aluminized biscuits. For example, he found an average of 1.7 mg. of aluminum, determined as Al_2O_3, per hundred grams of blood in three dogs fed aluminized biscuits for from fifty-five to sixty days. Calculated for an average rabbit weighing 3 kg., the daily injection of 0.04 Gm. of sodium aluminum sulphate ($Al_2[SO_4]_3.Na_2SO_4.24H_2O$) or 0.01 Gm. of aluminum chloride ($AlCl_3.6H_2O$) would constitute a comparable amount of aluminum ion in the blood stream.

Both of these solutions were acid: the 0.8 per cent solution of $Al_2(SO_4)_3.Na_2SO_4.24H_2O$ having a p_H of 3.4 and the 0.2 per cent solution of $AlCl_3.6H_2O$ Having a p_H of 3.8. Since acid is known to hemolyze blood cells, it was thought that the anemia produced by the

14. M'Neil, C.: J. Path. & Bact. **15**:56, 1910-1911.

injection of these aluminum solutions might possibly be due to the hydrogen ion concentration of the solutions. Sulphuric acid, therefore, of such strength that its p_H was 3.4, was injected intravenously into two rabbits for the same length of time as the aluminum solutions. Moreover, since sodium aluminum sulphate solutions liberate their acid slowly, a p_H determination does not indicate the amount of acid that is capable of being released, and therefore, a sulphuric acid solution of acidity corresponding to the maximal amount of acidity that could be liberated by the corresponding aluminum solution, namely, a p_H of 2.6, was also injected daily into two rabbits. It is not probable, however, that the tissues were ever subjected to such a high degree of acidity at any one time from the alum injected, for all of the acid would probably not have been released instantaneously, and the buffering action of the blood would have considerably diminished the acidity.

Results with $Al_2(SO_4)_3.Na_2SO_4.24H_2O$.—Five rabbits, no. 1 (3.6 Kg.), no. 2 (3.4 Kg.), no. 10 (2.4 Kg.), no. 15 (2.7 Kg.) and no. 20 (2.5 Kg.), which were given intravenous injections of 0.04 Gm. each of sodium aluminum sulphate ($Al_2[SO_4]_3.Na_2SO_4.24H_2O$) daily, all developed a secondary anemia after a period of from eleven to twenty days (chart 1). The percentage of hemoglobin always decreased considerably. The number of red cells per cubic centimeter showed an ultimate decline in every rabbit, except no. 15, extending as low as 1,870,000 in no. 1. The total number of leukocytes per cubic centimeter usually rose, reaching its peak, as high as 25,650, in rabbit 10, about the time that the number of erythrocytes per cubic centimeter was the lowest, and the increase was usually in the number of small mononuclear lymphocytes (chart 2). In order to save space the polymorphonuclear and mononuclear leukocyte curves for all five rabbits have been superimposed on each other and from these a single average curve computed and recorded.

The blood cells became more resistant to hemolysis as treatment continued (chart 3). In other words, a more hypotonic saline solution was required to hemolyze the cells, after treatment of the rabbit with aluminum compounds. This increased resistance of the blood cells to hemolytic agents was also demonstrated (to a slight extent) with saponin, for more saponin was necessary to hemolyze the blood at the end of the experiment than in the beginning.

A study of the blood cell picture (Wright's stain) revealed in all five rabbits a marked development of abnormal cells, similar to those found in lead poisoning. Some nucleated erythrocytes or normoblasts were always found in the later stages. Polychromasia, poikilocytosis and anisocytosis were marked. Stippled cells were found.

In addition to these definite indications of anemia, all five rabbits showed unmistakable symptoms of local aluminum poisoning. The

ears into the veins of which the aluminum solution was injected became edematous, inflamed and then necrotic, so much so that portions of the ears of some of the rabbits sloughed off. This, of course, was due to the irritant effects of the aluminum on the tissue or to thrombosis of the vessels, and was undoubtedly a local reaction. Swellings later

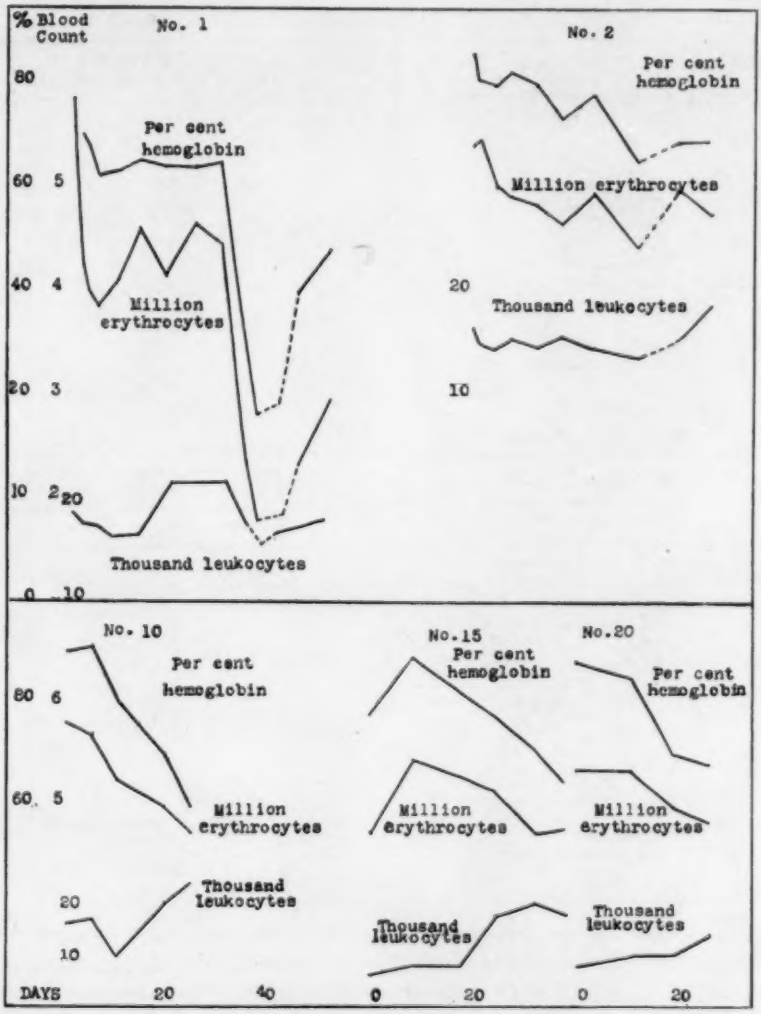

Chart 1.—The individual hemoglobin, erythrocyte and leukocyte curves of five rabbits following daily intravenous injection of 0.04 Gm. each of sodium aluminum sulphate.

appeared on the under side and the back of the neck and in the axillary glands in all five rabbits. The rabbits, as a whole, lost comparatively little weight, in spite of the development of roughened hair and a sickly

appearance. However, no. 1 lost 1⅜ pounds (1.2 Kg.) and gave the most marked reactions of all. The temperatures of nos. 1 and 2 never rose much above normal, while that of no. 10 reached 105.6 F. three days before its death, which was probably due to sepsis.

The toxic effects of injecting aluminum solutions are not surprising when the effects of aluminum on the blood in vitro are seen. When a

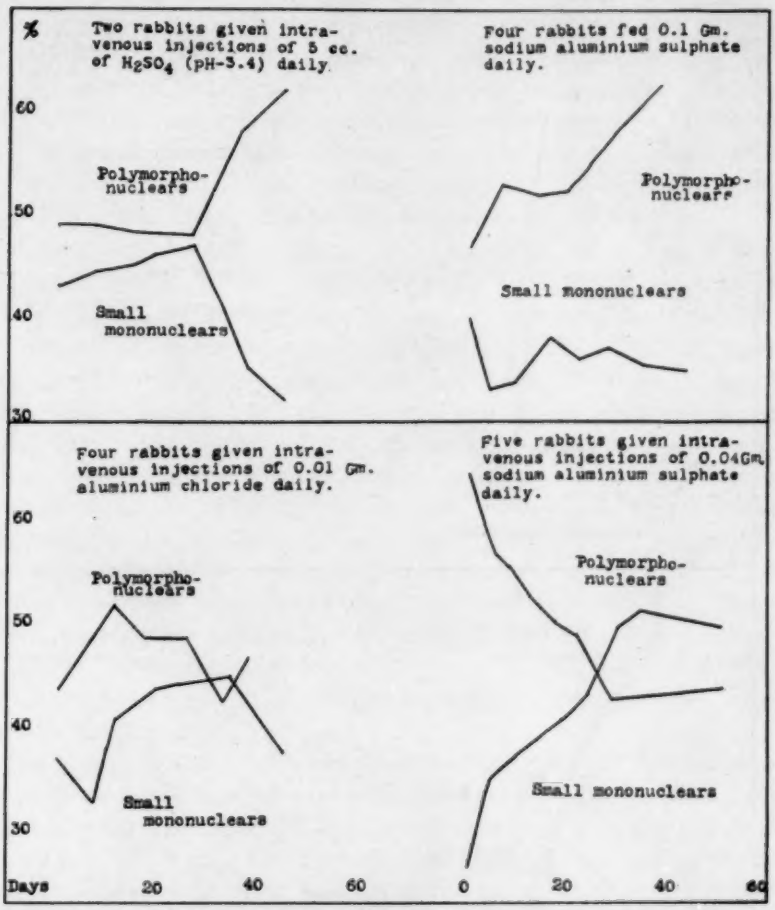

Chart 2.—The average leukocyte curves of rabbits following daily intravenous injection of sulphuric acid; daily intravenous injection of aluminum chloride; daily intravenous injection of sodium aluminum sulphate, and daily oral ingestion of sodium aluminum sulphate.

drop of fresh blood of a normal rabbit was placed in a small amount of a solution of sodium aluminum sulphate of the strength used for injections, almost immediately the hemoglobin was expelled from the corpuscles and decomposed to a brown hematin solution, and a white,

flocculent precipitate formed. When the blood was dropped into the solution of aluminum chloride, a clear brown hematin solution resulted. But when the blood was dropped into a sulphuric acid solution of a p_H of 3.4, no hemolysis occurred; in fact, the cells became closely packed in the bottom of the tube and remained there for days unhemolyzed.

Results with $AlCl_3.6H_2O$.—Four rabbits, no. 3 (2.7 Kg.), no. 9 (2.9 Kg.), no. 12 (2.7 Kg.) and no. 14 (2.4 Kg.), received intravenous

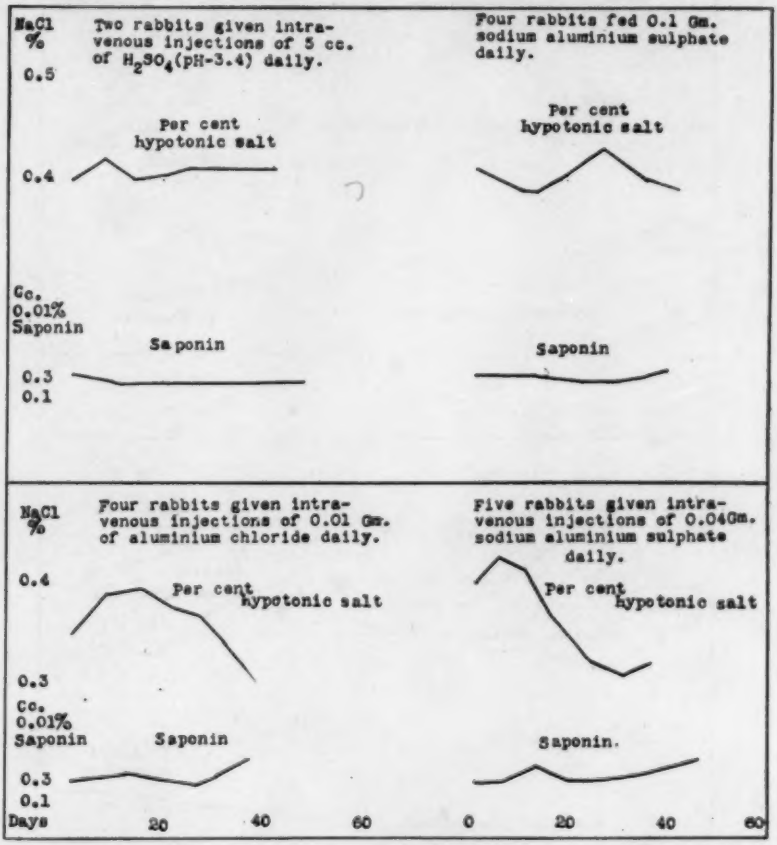

Chart 3.—The average curves for the hemolysis of red cells by hypotonic salt and saponin in rabbits treated with aluminum compounds (controlled by the curves of two treated with sulphuric acid).

injections of 0.01 Gm. each of aluminum chloride ($AlCl_3.6H_2O$) daily (chart 4). In every rabbit there was a marked decrease in homoglobin. In all but one, the resistance to hemolysis increased in the later stages (chart 3). The number of erythrocytes fell somewhat in all except no. 12. At certain times, all showed a definite leukocytosis, and in nos. 3, 12 and 14 the increase seemed to be in the number of the small

mononuclear lymphocytes (chart 2.) Abnormal blood cells, chromatophilic cells, poikilocytes, anisocytes and normoblasts were found in the later stages, as in the blood of rabbits treated with sodium aluminum sulphate ($Al_2[SO_4]_3.Na_2SO_4.24H_2O$). The experiment on rabbit 9 was discontinued sooner than usual because of the development of an

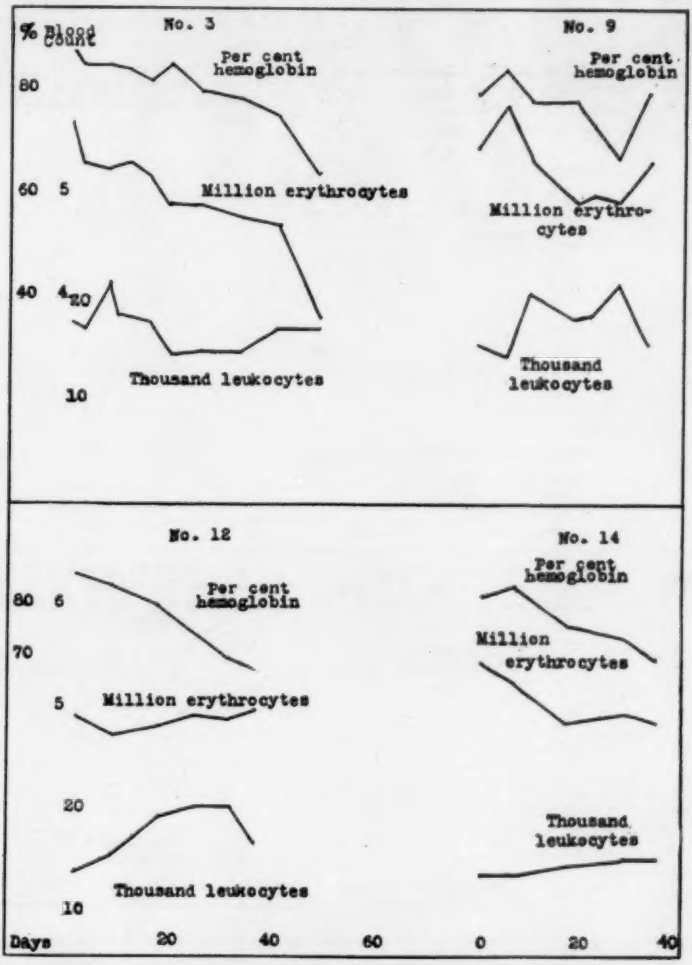

Chart 4.—The individual hemoglobin, erythrocyte and leukocyte curves of rabbits following daily intravenous injection of 0.01 Gm. each of aluminum chloride.

infection in the inner ear. In all four rabbits, swelling, edema, inflammation and necrosis of the ears appeared as soon and almost to the same extent as in rabbits treated with sodium aluminum sulphate. Nos. 3 and 12 in the later stages displayed swellings on the under side and

on the back of the neck. There was practically no loss of weight in any of the rabbits, but all became quiet and sickly.

Results of Control Injections of Acid Solutions.—Two rabbits, no. 5 (3.6 Kg.) and no. 11 (3 Kg.), for forty-five and thirty-six days, respectively, received daily intravenous injections of 5 cc. each of a sulphuric

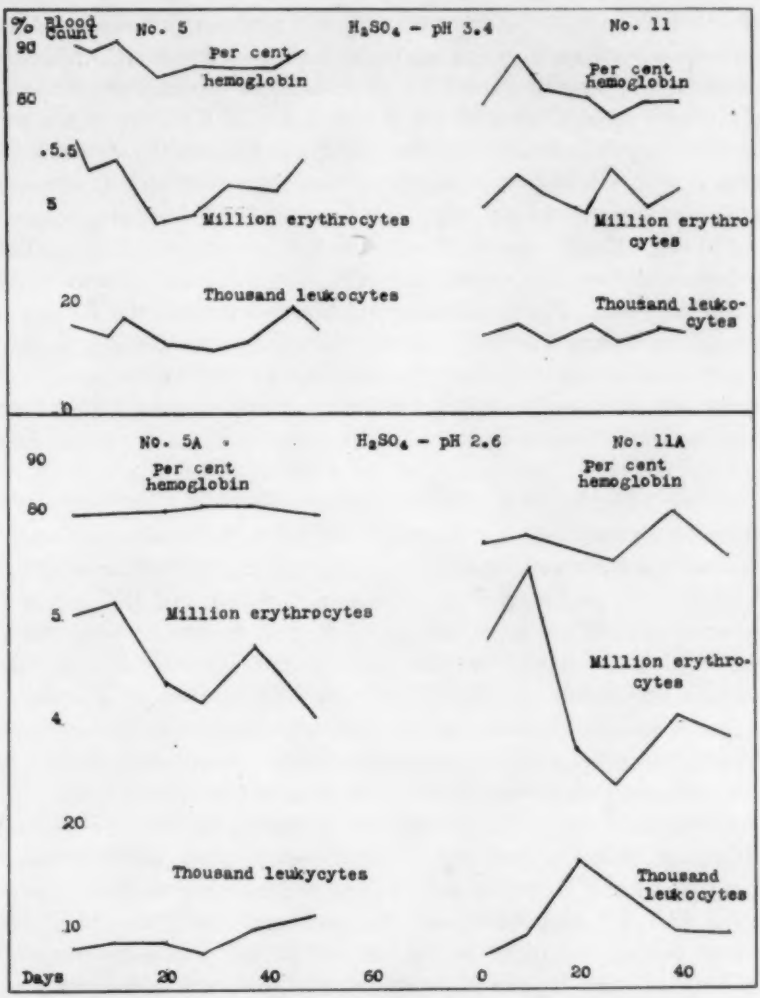

Chart 5.—The individual hemoglobin, erythrocyte and leukocyte curves of rabbits following daily intravenous injection of 5 cc. each of sulphuric acid.

acid solution of such strength that its p_H was 3.4. As indicated before, this was found to be the p_H of the 0.8 per cent solution of sodium aluminum sulphate injected (chart 5). At the end of and during these periods both rabbits appeared sleek and in perfect health and did not show any

of the marked symptoms or blood pictures described as occurring in the former groups of experiments.

Since more acid is liberated from sodium aluminum sulphate when it comes in contact with tissue than is free in the original solution, it is possible that some of the harmful effects reported following injections of the aluminum solution may be due to the acid liberated after the solution was injected. Therefore, sulphuric acid solution with a p_H of 2.6, which corresponds to the maximal amount of acid which can be liberated by the sodium aluminum sulphate, was injected intravenously daily into two rabbits, 5A (2.7 Kg.) and 11A (2.7 Kg.), for forty-nine days (chart 5). It is improbable, however, that this amount of acid would ever be free in the blood stream at any one time following injection of sodium aluminum sulphate solution because of the buffering capacity of the blood. There was no decrease in the percentage of hemoglobin, and there were no abnormal blood cells, but the total number of red cells did decrease. For a while during the experiment, the ear of one rabbit (11A) became swollen, owing to the irritant effects of the solution injected, and during this time the number of leukocytes rose. The other rabbit was in perfect health throughout the experiment and showed none of these symptoms.

THE LETHAL DOSE OF SODIUM ALUMINUM SULPHATE

Since the five rabbits that had received injections of sodium aluminum sulphate were able to tolerate for a considerable length of time daily doses of about 5 cc. containing 0.04 Gm. of the salt in 0.8 per cent concentration, it seemed of interest to determine what amount of the compound given in this way was lethal and in what concentration. Therefore, one rabbit (1.8 Kg.) was given an intravenous injection of 10 cc. of a solution containing 0.25 Gm. of sodium aluminum sulphate in 2.5 per cent concentration. Immediately, the rabbit's back bowed, and it cried, became limp, stopped breathing and died in spasms.

Another rabbit (1.8 Kg.) was then given an injection of the same total amount (0.25 Gm.) of sodium aluminum sulphate, but this time the salt was given in a large volume of solution or a weaker concentration, namely, 32.5 cc. of solution of 0.8 per cent strength. The rabbit trembled during the injection of the last 10 cc., but soon recovered completely. Three days later the rabbit was given 0.32 Gm. in 40 cc. in the same concentration over a period of two hours and the following day 0.16 Gm. in 20 cc. The rabbit did not collapse, but from then on it seemed to decline and became more quiet than normal, and its coat was roughened. Twenty-four days later it was found dead, having received a total of 0.73 Gm. in 72.5 cc. of a solution of a concentration of 0.8 per cent. At autopsy, petechiae were found in the mucosa of the stomach. The intestinal mucosa was red and microscopically showed

small areas of necrosis and mitosis in numerous epithelial cells. The spleen was small and fibrous, and microscopically it showed fibrosis and extensive necrosis of the pulp.

A third rabbit (1.6 Kg.) was given an intravenous injection of 10 cc. of 0.8 per cent solution (or 0.08 Gm.). Immediately, it showed slight symptoms of collapse. Eleven days later, it received the same dose and manifested no symptoms. Four days after this, it received five injections of 10 cc. each of a 1 per cent solution at hourly intervals and still showed no symptoms. The following morning, immediately after a single injection of 10 cc. of a 1 per cent solution, it died. This rabbit therefore died after receiving a total of 0.76 Gm. of the aluminum compound. At autopsy, extensive necrosis was found in the splenic pulp and some spontaneous nephritis, but no abnormalities of the alimentary tract.

Therefore, it can be stated approximately that a rabbit weighing 1.5 Kg. will survive an intravenous injection of 0.7 Gm. of sodium aluminum sulphate, if given in an 0.8 to 1 per cent concentration, but will be killed by any amount over this, given in a short period of time. And if the salt is more concentrated, the rabbit will not tolerate nearly so large an amount. However, small daily doses (5 cc.) of a solution of 0.8 per cent can be tolerated up to sixty days and longer, or until, as was the case in several of the rabbits receiving the injections, the rabbit is moribund and no longer offers a superficial vein for injection because of the necrotizing effect of the solution of aluminum on the surrounding tissues.

ANATOMIC STUDY OF THE RABBITS FED OR GIVEN INJECTIONS OF SMALL DOSES OF ALUMINUM

A careful study of the anatomic changes in the rabbits given injections of sodium aluminum sulphate and aluminum chloride, as compared with the control animals (those given injections of sulphuric acid solutions of corresponding acidity or fed lactose), revealed only one type of injury as certainly due primarily to the treatment, namely, pigmentation, thrombosis, necrosis and fibrosis in the spleen. On the whole, the spleens of the rabbits fed or given injections of the aluminum compounds were more heavily pigmented than were the spleens from the control rabbits given injections of sulphuric acid. However, later study of the spleens from rabbits fed only lactose and considered as normal revealed considerable pigmentation in three of four cases. It is true that necrosis of the splenic pulp cells was found only in the rabbits receiving injections of the solution of sodium aluminum sulphate, and this was extremely marked in several of these animals. The fact that there was such marked necrosis in the splenic pulp in the animals receiving large doses of alum, and that pigmentation and fibrosis were found so frequently

in the other animals, suggests the probability that the hemagglutinative effect of aluminum may be responsible for these changes in the spleen.

Some of the alimentary changes, such as petechiae and ulcers of the stomach and intestinal mucosa, probably had some relation to the treatments with alum, since they were found chiefly in those rabbits fed aluminum or given injections of it, even though they were not found constantly. This view is supported by the fact that similar intestinal lesions were found in mice fed alum by Schaeffer, Fontés LeBreton, Oberling and Thivolle.[5]

Focal necrosis of the liver cells seemed to be associated chiefly with infections, for example, bronchitis and pneumonia, and therefore it was found chiefly in the rabbits that had died of infections and cannot be attributed to the alum.

In summing up the microscopic study of the tissues of the twenty-six rabbits used in these experiments, it can be said that many of the pathologic lesions are not necessarily to be accredited to the treatment with aluminum compounds, since so many similar abnormalities were found in supposedly normal rabbits. The severe lesions in the spleens, however, for instance, the fibrosis and the necrosis, of even those rabbits receiving small daily doses of alum were probably due to the treatment with aluminum. The marked changes (to be described later) in the kidneys of the rabbits fed large doses of aluminum compounds and the extensive vacuolization and granular degeneration of renal epithelium in the rabbits fed small daily doses or given intravenous injections of sodium aluminum sulphate for a long period of time were not to be found in any of the control rabbits and were therefore, presumably, truly an aluminum effect. The agglutination thrombi found in the lungs, liver and kidneys of some of the animals were also never observed in the control rabbits.

EFFECTS OF FEEDING OF ALUMINUM

The experiments in this part deal with the effects following the feeding of small daily doses of sodium aluminum sulphate to rabbits over short periods (two months) and over long periods (up to one year); and the effects following the feeding of a single large dose or a few large doses of different aluminum compounds.

FEEDING OF SMALL DAILY AMOUNTS

Eight rabbits, nos. 8 (4.07 Kg), 16 (3.2 Kg.), 17 (2.5 Kg.), 35 (2.5 Kg.), 36 (2.5 Kg.), 37 (2.7 Kg.), 61 (2.8 Kg.) and 500 (4.07 Kg.), were each fed daily a gelatin capsule containing 0.1 Gm. of sodium aluminum sulphate ($Al_2[SO_4]_3.Na_2SO_4.24H_2O$) mixed with powdered lactose. This amount of the salt fed to a rabbit weighing 4 Kg. is comparable with the amount fed by Kahn to dogs. For example,

he fed 15 Gm. of aluminized biscuit per kilogram, and his analyses show that this amount of biscuit contains 2.4 mg. of Al_2O_3, which is equivalent to 21.53 mg. of sodium aluminum sulphate ($Al_2[SO_4]_3.NA_2SO_4.24H_2O$). In the case of four rabbits, the feeding was continued for only a short period, up to sixty days, and in the case of four others the feeding lasted from 150 to 350 days. In all except Nos. 35 and 37 (charts 6 and 7) the percentage of the hemoglobin

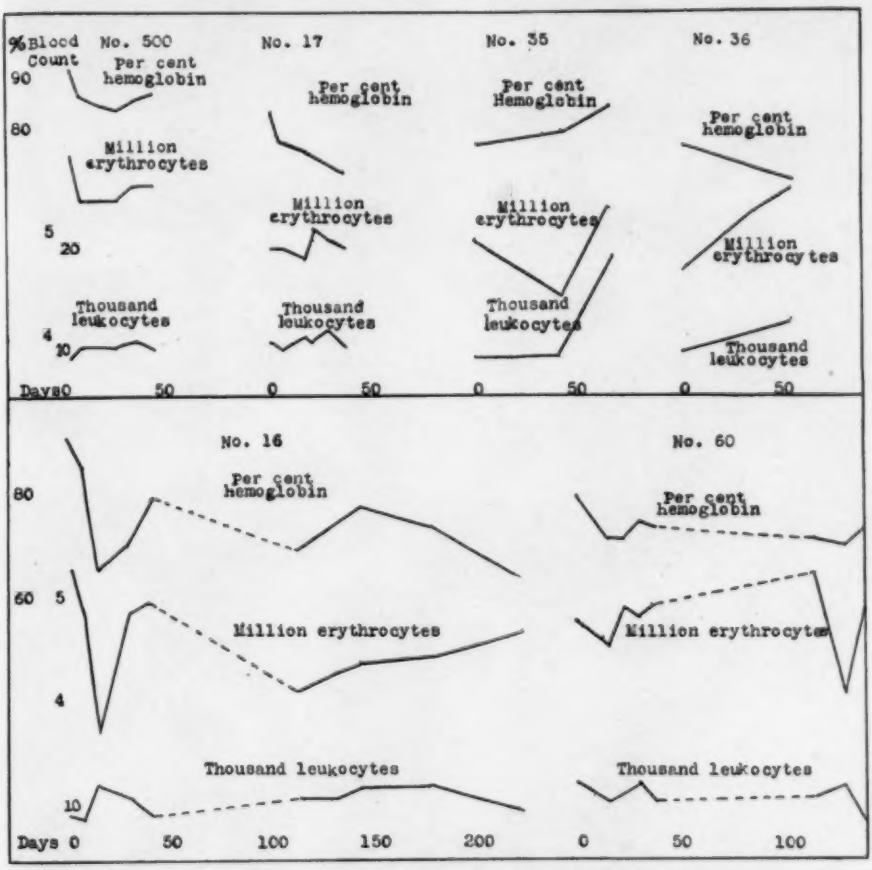

Chart 6.—The individual hemoglobin, erythrocyte and leukocyte curves of rabbits fed daily 0.1 Gm. each of sodium aluminum sulphate. The dotted line represents a period during which the feeding of the aluminum salt was suspended.

decreased, during the experiment, more than in the control rabbits (chart 8) fed only lactose. These two rabbits, nos. 35 and 37, as well as no. 36, showed a decided increase in the number of erythrocytes, comparbale to that in the control rabbits fed lactose. An explanation

of this phenomenon is wanting. It is noteworthy that in many of the alum-fed rabbits, especially rabbits 35, 16, 60 and 8, periods of marked depression of the number of erythrocytes are followed by periods of a rise in their number. There was practically no change in the total number of the leukocytes.

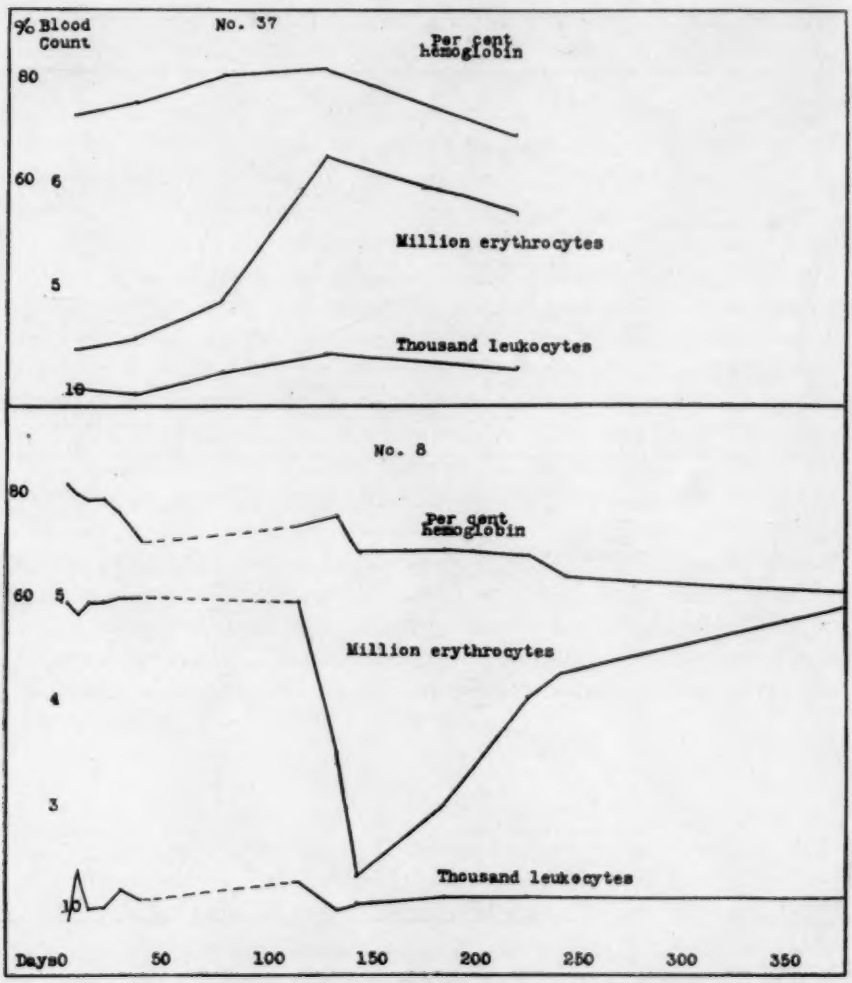

Chart 7.—The individual hemoglobin, erythrocyte and leukocyte curves of rabbits fed daily 0.1 Gm. each of sodium aluminum sulphate. The dotted line represents a period during which the feeding of the aluminum salt was suspended.

Whether this somewhat consistent decrease in percentage of hemoglobin and the occasional marked depression in the number of erythrocytes is mere chance or whether it is significant may possibly be

decided by noting whether any considerable effects follow the feeding of large doses. If acute effects can be produced by the latter means, then are we not justified in suspecting that slight similar effects repeated over years may lead to chronic symptoms with a gradual failing of the hematopoietic system and the attending lowered resistance? It seemed worth while, therefore, to study the effects following the feeding of large doses of aluminum.

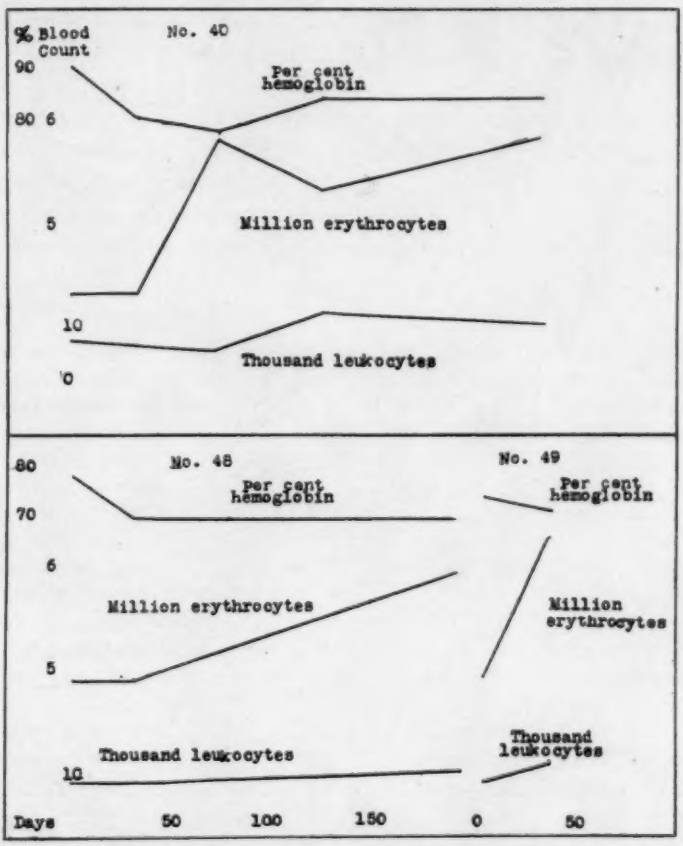

Chart 8.—The individual hemoglobin, erythrocyte and leukocyte curves of rabbits daily fed lactose only. These were controls on the rabbits fed sodium aluminum sulphate, which was mixed with lactose.

FEEDING OF A SINGLE LARGE DOSE OR A FEW LARGE DOSES OF ALUMINUM COMPOUNDS

Results with $AlCl_3.6H_2O$.—Rabbit 55 (1.5 Kg.) was fed 1.5 Gm. of aluminum chloride ($AlCl_36H_2O$) in gelatin capsules. In fifteen minutes, it began to breathe hard, displayed the motions of vomiting, stretched at length prostrate and jerked its head from side to side. It

then seemed to improve for a while, but after two hours died in convulsions. Autopsy revealed much liquid, containing aluminum, in the stomach, much mucous secretion and black hemorrhagic areas on the mucosa. The fluid in the stomach darkened blood when it came in contact with it, as does the aluminum ion.

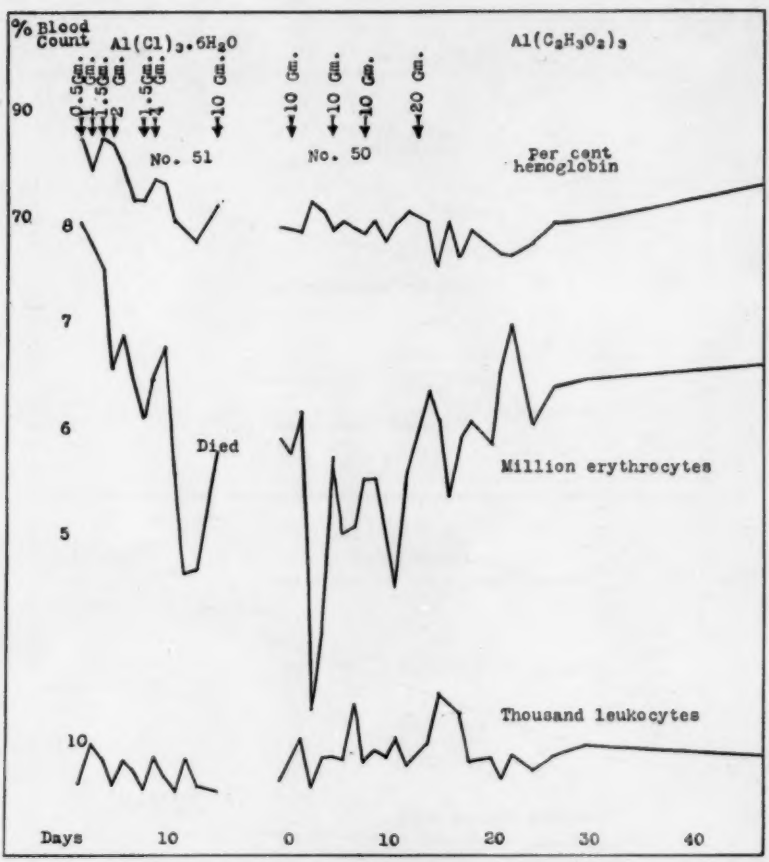

Chart 9.—The individual hemoglobin, erythrocyte and leukocyte curves of two rabbits following the feeding of single large doses of aluminum compounds over a period of fourteen days. An arrow indicates the time and the amount of each feeding.

Another rabbit, no. 51 (3 Kg.), was fed large single doses of aluminum chloride in gelatin capsules, ranging from 0.5 to 10 Gm. during a period of fourteen days. On chart 9, the arrows indicate the times of feeding and the amounts are mentioned. The total fall of over 3,000,000 in the number of erythrocytes and the fall of 18 per cent in hemoglobin, as well as the individual decreases after each dose, are striking. It is

noteworthy that the effect is registered soon after each feeding. This is indicative of a real toxicity of the aluminum, rather than of an impairment of digestive functions, which would lead to similar changes only later. There was no loss in weight. The rabbit finally died as a result of a feeding of 10 Gm.

The autopsy was performed within less than two hours after death. There were hemorrhages in the stomach, the mucosa of the whole small intestine was blanched, as if macerated, and there was a complete loss in tonus of the entire tract. The spleen was spongy, flabby and engorged; the kidney was small and soft and the cut surface was abnormal.

Microscopic examination showed marked changes in the kidney, which were essentially the effects produced by toxic agents. Changes suggesting the same condition were found in the spleen, and the lesions in the spinal cord were especially interesting.

The detailed protocols of the microscopic observations in rabbit 51 follow:

The liver was normal.

The spleen showed slight fibrosis of the pulp and slight diffuse pigmentation. In the pulp was blood pigment in phagocytes. Occasionally, large phagocytes contained both pigment and cells: also there were occasional areas of coagulated material not containing cells. There were numerous clumps of cells resembling somewhat cellular thrombi, although no distinct vessel wall could be seen about them, and there were also areas of hemorrhagic infiltration of the pulp.

The kidney showed swollen convoluted tubules, with, as a rule, no lumen remaining. There was practically no staining of nuclear material in the cells of the convoluted tubules. The epithelial lining appeared as solid coagulated masses, generally shrunken from the basement membrane. Loss of staining was so complete as to resemble an advanced postmortem autolysis, which can be excluded by the fact that the animal was sectioned two hours after death. Furthermore, the fusion of the renal epithelium into solid, structureless, granular masses, in places resembling granular casts, indicates that there had been a marked antemortem destruction of the swollen epithelium of the convoluted tubules in toto. Rarely, a cell was found in the convoluted tubular epithelium that retained nuclear stain. The nuclei of the basement membrane of these same tubules stained well, as did the nuclei of the loops of Henle, although these cells were swollen and often separated from one another. The collecting tubules showed swollen epithelium, the lumen rarely being visible, but the nuclei stained well. The glomeruli retained their nuclear staining. The tufts were generally swollen, but no hemorrhage or exudation was seen. The appearance indicated a selective toxic necrosis of the epithelium of the convoluted tubules.

The spinal cord showed marked destruction of the cytoplasm of many of the ganglion cells, some of which exhibited little besides the nucleus, containing many vacuoles and a granular detritus filling up the space formerly occupied by the ganglion cell. All the ganglion cells were more or less affected the same way. The white matter was also greatly vacuolated and granular.

The lung contained many small hemorrhages, slight edema and marked engorgement of the vessels. There was no inflammatory reaction. The red corpuscles seemed to be discrete, and hyaline thrombi were not recognized.

The stomach showed a diffuse loss of nuclear stain. There was no sharp necrosis, no inflammatory reaction. The vessels were engorged with blood.

The adrenal glands stained well and showed no recognizable alterations.

The duodenum showed a necrotic condition of the superficial portion extending about half through the mucosa, accompanied by a marked accumulation of stringy, blue-staining material, apparently mucin. There was no inflammatory reaction.

Lest the effects observed in these two experiments might be solely due to the acid liberated from the chloride compound, other aluminum compounds were similarly used.

Results with $Al(C_2H_3O_2)_3$.—Rabbit 50 (3.8 Kg.) was fed four times, at five day intervals, 10 Gm. of $Al(C_2H_3O_2)_3$ in approximately 100 cc. distilled water by stomach tube (chart 9). Before each feeding, the rabbit had been starved over night to insure a fairly empty stomach. In this experiment, the decrease in the number of erythrocytes after each feeding is striking, but not lasting, and in the final rebound the level is higher than it was originally. The percentage of hemoglobin is not seriously lowered, although there is evidence of a slight decrease after some of the feedings. Thirty-three days after the fourth feeding, this animal was killed by a blow on the back of the head and examined immediately. The histologic observations were as follows:

The lungs showed no change.

The liver showed slight fatty degeneration in the liver cells, nowhere marked, but diffuse through all parts of the lobule. There were vague masses staining red with scarlet R, some of which were in the blood vessels and some in the sinusoids. The nature of these is not clear, but their location raises the question whether they can be agglutination thrombi. A section of the same liver stained with hematoxylin and eosin showed in some of the vessels masses of fused red corpuscles corresponding in shape and size to the masses that stained red with fat stains. When the specimen stained with scarlet R was counterstained with hematoxylin, it was seen that some of the fat masses corresponded to large, fatty liver cells or to Kupffer's cells, but there were also masses staining like fat which plugged the sinuses.

The heart showed no change, and no fatty degeneration.

The duodenum showed diffuse loss of staining in its surface layers, occasional submucous hemorrhages. The excretory ducts of a few of the Brunner's glands were packed with leukocytes, although there were no changes in the adjacent tissues.

The adrenal glands revealed no change.

The spleen was generally normal in structure, except for occasional accumulations of brown pigment in masses, not generally in phagocytes.

The stomach was normal.

The kidney presented epithelium somewhat swollen and vacuolated. There was no fatty degeneration of the epithelium, but there were occasional irregular masses of fat stain, the location and nature of which could not be accurately determined.

Rabbit 730 (2 Kg.) was fed 30 Gm. of Al $(C_2H_3O_2)_3$ in a single dose in 100 cc. of water by stomach tube. Although it seemed to be all right following the feeding, on the third day it was found dead. At autopsy, the adrenal gland was normal. The spleen was small, thin and somewhat congested in areas. The stomach was filled with a brownish watery suspension, the muscles lacked tonus and the mucosa was completely coagulated into granular white folds. The small intestine seemed normal, but was filled with a jelly-like, yellowish-green substance. The heart was somewhat distended with venous blood, and showed profound fatty degeneration. In the lungs were many patches that looked extremely hemorrhagic and these were interspersed with pale areas. On cutting, much dark blood oozed out. The microscopic observations were as follows:

In the lung, areas of edema were present without inflammatory change, and the vessels were engorged with blood. The testicle showed no spermatogenesis. There was no atrophy, but the spermatids and spermatozoa were entirely lacking. Many large multinucleated cells were present in the tubules. The epididymis contained no spermatozoa. The kidney showed profound fatty degeneration in all the straight tubules; the epithelium was much swollen, granular and finely vacuolated, occluding the lumen. Fat droplets were present in the convoluted tubules and glomeruli and also in the intima of the blood vessels. In the liver were branching streaks that took the fat stain, and the size and location of these streaks corresponded to those of the capillaries, but there was no fat in the liver cells. The fat masses were generally too large to correspond to the Kupffer cells. In the centers of some of the lobules, however, there was slight fatty degeneration in the liver cells. In some places, where the capillaries contained blood, the material that stained like fat could be seen definitely to be in the walls of the blood spaces. The sinuses of the spleen were much dilated and contained many granular masses and some resembling agglutinated red corpuscles as well as distintegrated red corpuscles. There were masses of mucus present on the surface of the stomach and extending slightly into the lumen of many of the glands. The glands near the surface were disorganized, but no inflammatory changes were seen.

Results with Metallic Aluminum.—Rabbit 53 (2.5 Kg.) was fed only two doses (3 and 4.5 Gm.) of powdered metallic aluminum in gelatin capsules (chart 10). The fall of 2,000,000 in erythrocytes and of 22 per cent in hemoglobin is good evidence that the aluminum goes into solution in the digestive juices and is absorbed. These decreases are further evidence that the changes in the blood noted in some of the previous experiments were due to the aluminum ion itself rather than to any acid radical accompanying it. Thirty-nine days after the last feeding, this rabbit was killed by a blow on the head and examined immediately. Few pathologic changes were noted. In the kidney, the renal epithelium was slightly swollen and granular, but the lumen usually persisted and in some of the tubules the epithelium was much vacuolated. There were no casts. Marked fatty changes were seen in the Kupffer cells, but no fat was seen in the liver cells.

Rabbit 771 (2 Kg.) was fed metallic aluminum in the following doses on four consecutive days: 2, 1.7, 2 and 2.1 Gm., respectively. Twenty days after the last feeding the rabbit was found dead, and the autopsy indicated that death was probably due to an infection of the lungs. The spleen was small and dark; the stomach and duodenal mucosa were blanched and the stomach was filled with gas.

Microscopically, the spleen was enormously engorged with blood, and the sinuses were greatly distended with blood, but without thrombosis or necrosis. The lungs showed acute suppurative pleuritis, which may account for the focal

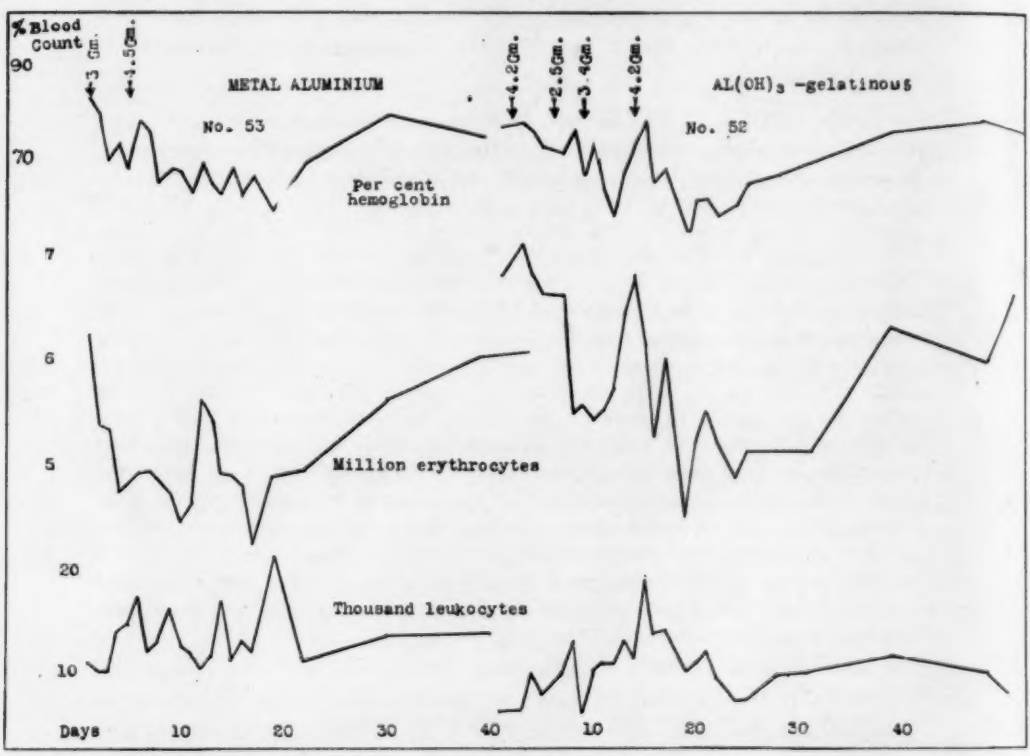

Chart 10.—The individual hemoglobin, erythrocyte and leukocyte curves of two rabbits fed aluminum compounds as follows: rabbit 53, metallic aluminum, and rabbit 52, $Al(OH)_3$ (gelatinous). An arrow indicates the time and the amount of each feeding.

necrosis in the liver. The tubular and cortical epithelium of the kidney was swollen and the glomeruli were much engorged with blood. In the liver, the centers of the lobules showed a decreased number of cells and loss of cord arrangement, and the liver cells here seemed somewhat coagulated, although they preserved their nuclei, which tended to be pyknotic. There were small areas of early focal necrosis and fatty changes in some of the Kupffer cells without fat in the liver cells.

Results with $Al(OH)_3$.—Since the aluminum ion, as it is usually ingested with foods, is chiefly in the form of Al $(OH)_3$, rabbit 52 (2.75Kg.) was fed with $Al(OH)_3$,[15] suspended in from 50 to 100 cc. of distilled water.

This suspension was fed by stomach tube to the fasting rabbit, over a period of from two to five hours, according to its ability to tolerate the aluminum. The accompanying curves of rabbit 52 (chart 10) show that this compound was apparently absorbed just as were the other aluminum compounds. The drop of 2,600,000 in erythrocytes and of 20 per cent in hemoglobin is evidence that the compound does not all pass on through the alimentary tract as inert material. When this rabbit was killed forty days after the last feeding no pathologic changes were found, gross or microscopic.

Rabbit 750 (2.5 Kg.) was fed, at one time, by stomach tube, 40 Gm. of $Al(OH)_3$ suspension prepared in the same manner as that described for the preceding experiment. At the end of three days, it was moribund. It was killed with ether and examined immediately. The stomach contained nothing except a watery mucous substance filled with dark brown blood clots, some of which were also on the mucosa. The same condition was observed in the duodenum. The lungs also contained hemorrhagic spots, and red and white patches. The blood was almost black, and ran freely. Otherwise, the tissues were normal.

The microscopic changes noted were chiefly those of fatty degeneration. In the kidney, the convoluted tubules and Henle's loops were chiefly involved, and the collecting tubules and the pyramids showed but slight fatty changes. The blood capillaries were often filled with agglutinated and hemolyzed red corpuscles, forming thrombi. The glomeruli showed only occasional dustlike fat droplets. Homogeneous pink-staining material was found in the vessels of the heart and of the liver and marked fatty degeneration of the parenchyma cells was present. In the liver, the degeneration was least marked about the portal triads. In the lung, a few of the bronchioles contained leukocytes, but there were no pneumonic changes. A few leukocytes were found in the alveoli and alveolar walls. The blood in the small vessels had a brassy appearance, and in some it was hemolyzed. The testicle seemed normal. In the stomach was an area of superficial ulceration, in which were many polymorphonuclear leukocytes. These extended into many of the gastric glands, even those at considerable distance from the site of the ulcer. There were many mitotic figures in the glandular epithelium in this vicinity. The spleen was poor in lymphoid tissue and the pulp diffusely fibrotic. There was much brown pigment. There were many small masses of iron and extensive deposits in the capsule and trabecula, but only a faint iron stain in many of the phagocytes. The larger masses of dark brown material did not stain for iron.

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15. The $Al(OH)_3$ was prepared as follows: 50 Gm. $Al_2(SO_4)_3.Na_2SO_4.24H_2O$ was dissolved in distilled water. Enough strong sodium hydroxide was added to neutralize the solution and to precipitate the aluminum as $Al(OH)_3$ in the form of a gelatinous mass. This precipitate was then filtered off and washed with hot water to free it from other soluble salts. The washed precipitate was then ground to a creamy paste in a mortar with about 100 cc. of distilled water.

Again 45 Gm. of a suspension of $Al(OH)_3$, made as previously described, was fed to rabbit 775 (2.3 Kg.) by stomach tube. The rabbit died suddenly four days later, probably from peritonitis caused by a perforation in the stomach, which was full of a black mash intermingled with some loose, white, mucous masses. There was considerable hemorrhage around this perforation. The lungs were full of raised white patches and dark red areas.

Microscopically, no changes were found in the liver, testicle, lungs and spleen (except postmortem changes). A few glands in the duodenum were dilated. The kidney showed marked postmortem changes. The peripheral portion was well fixed, but showed no definite changes, and there were also no fatty changes, as determined by special staining, except that the protoplasm of the epithelium of the convoluted tubules stained diffusely a little more than other elements.

$Al(OH)_3$ may exist in two forms—either as a gelatinous compound, which readily dissolves in the slight acidity or alkalinity of the digestive juices, or in a more granular form, which is supposed to be extremely insoluble. Two more experiments were therefore planned. For these, the solution containing 50 Gm. of sodium aluminum sulphate ($Al_2[SO_4]_3.Na_2SO_4.24H_2O$) was neutralized, changing it to $Al(OH)_3$, and washed, and the final suspension of gelatinous $Al(OH)_3$ was boiled two hours over a direct flame to change it to the granular, insoluble form. This process is comparable to what might happen to a greater or less extent in baking.

Rabbits 54 to 56 were fed by stomach tube with three doses each of this compound and chart 11 shows that even this presumably insoluble compound must have been absorbed, for the effects on the erythrocytes and the hemoglobin were similar to those obtained in the former experiments.

Rabbit 56 (2.7 Kg.) was fed its third dose of $Al(OH)_3$ at 4 p. m., and at 10 p. m. it seemed to be perfectly normal, with the exception of a slight diarrhea. (Rather severe diarrhea frequently followed some of the feedings.) The next morning, the rabbit was found dead. At autopsy, the stomach was found to be full of a brown mush mixed with a white, slimy precipitate, and the wall was thin and hyperemic. The small intestines were filled with a watery brown mixture, and the colon was distended with a thin, watery brown liquid.

Microscopically, the changes in the kidney resembled those found in another rabbit (51), which died as a direct effect of feeding aluminum chloride ($AlCl_3.6H_2O$). In the lungs, agglutination thrombosis was found, so extensive as to have been the probable cause of death. This is significant in connection with death from ingested aluminum, for it has been shown that aluminum is a strong agglutinating reagent with red corpuscles. The protocols of the histologic examinations follow:

The epithelium of the kidneys was swollen so that the lumen was often occluded. Occasionally, granular casts and loose cells were seen. Many of the cells of the convoluted tubules contained yellowish-brown material in granules, sometimes occupying vacuoles. It was not as dark brown as hemosiderin and had more the appearance of hemoglobin. A large proportion of the convoluted tubules showed this change. There were occasional hyaline casts and occasional tubules in which the epithelial cells were disintegrated and lay in loose masses filling up the tubules. There was no frank coagulation necrosis. The glomeruli generally seemed to be normal. The collecting tubules had swollen epithelium, but otherwise seemed normal.

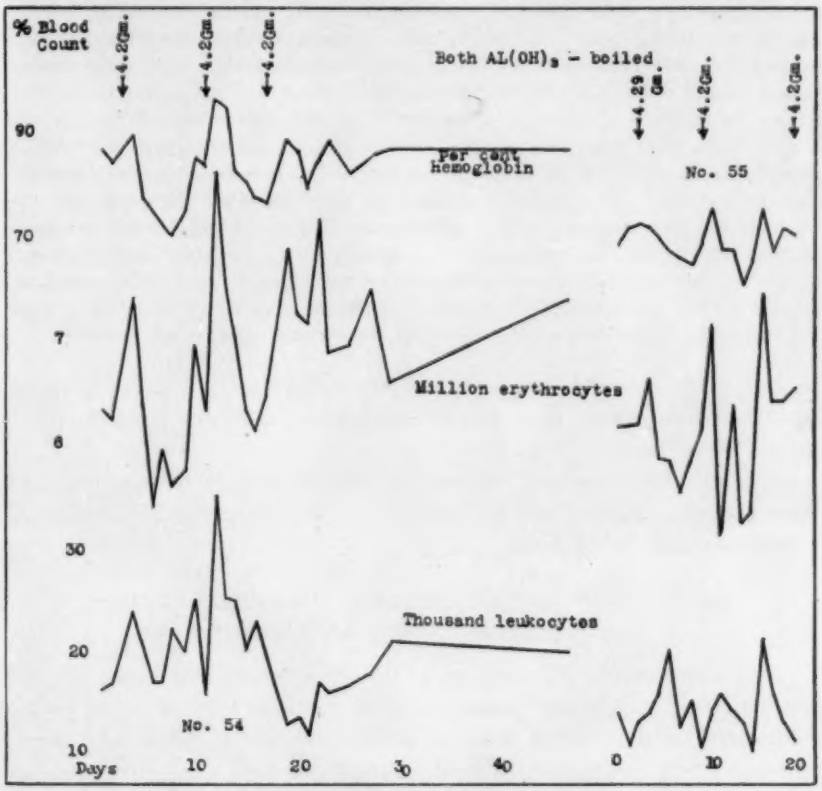

Chart 11.—The individual hemoglobin, erythrocyte and leukocyte curves of rabbits fed three large single doses each of a boiled aluminum compound $Al(OH)_3$ in the amounts and at the intervals indicated by the arrows.

The adrenal glands were normal.

The lungs showed marked engorgement of vessels with occasional small hemorrhages into the alveoli and edema involving perhaps one fourth of the alveoli. Some of this edematous fluid was also present in the bronchi. The capillaries were distended with masses of homogeneous structure, apparently thrombi from agglutination of red corpuscles. In the larger vessels, the red corpuscles were usually discrete. This condition of capillary agglutination thrombosis was extremely marked. There was no inflammatory process.

The myocardium was normal.

The stomach showed diffuse loss of stain on the surface, apparently postmortem.

The pancreas and the duodenum revealed no changes.

The spleen showed no pigmentation, hemorrhage or necrosis, except for an occasional phagocytic cell containing brown granules. The fibrous elements of the pulp were more conspicuous than usual.

The testicle showed spermatogenesis present but not abundant.

When the other rabbit, no. 54 (2 Kg.), which was fed boiled Al $(OH)_3$ also was killed, the tubular epithelium of the kidneys was generally normal, but in a few of the glomeruli, the capillaries were distended and contained homogeneous red cells, apparently thrombi from agglutination, but no hemorrhage or exudation. There was slight fatty degeneration in a few of the convoluted tubules and the endothelial cells. A few of the capillaries were plugged with masses staining for fat. The capillaries of the lungs were distended with homogeneous masses of red cells—agglutination thrombi—but there was no edema or hemorrhage. In sections of the liver stained for fat and counterstained with hematoxylin, there were many red masses corresponding in size and shape with single large liver cells, each with an intact nucleus surrounded by a solid mass of fat droplets, although the great majority of the liver cells contained no fat despite the fact that all the cells were deeply vacuolated. There were also smaller masses of stain that seemed to correspond to Kupffer's cells. Another section showed masses of fat granules, some corresponding to enlarged liver cells, others to Kupffer's cells, the latter being especially conspicuous in this liver. There were also masses of agglutination thrombi filling sinuses and small blood vessels.

The effects on the leukocytes in these rabbits fed large doses of aluminum compounds were plotted (chart 11) also, and occasionally a marked disturbance was noted.

A study of the blood pictures in these animals showed marked polychromasia, slight poikilocytosis and anisocytosis and an occasional normoblast and stippled cell.

EFFECT OF ALUM ON THE PRODUCTION OF COMPLEMENT AND ANTIBODIES

The experiments to determine the effects of aluminum on the production of complement and antibodies fall into four groups. Group 1 consisted of the control tests, in which one rabbit, no. 7 (2.7 Kg.), received a single injection of 5 cc. of a 50 per cent solution of washed sheep cells, and two rabbits, nos. 23 (2.9 Kg.) and 24 (2.8 Kg.), each received two injections of sheep cells seven days apart. Hemolysins and agglutinins were followed in each rabbit (chart 12). The development of agglutinin was followed by not adding complement to every other tube in the titration. A small amount of hemolysin was found following a single injection of sheep cells; but practically no agglutinin was demonstrable. There was a sudden rise, however, in both antibodies following a second injection of sheep cells. The chart shows, furthermore, an increase in native complement (fine dotted line in chart), following the second injection of sheep cells. The experiments are reported because

the contrast is so great between the results in groups 1 and 2 and those in groups 3 and 4 (with rabbits receiving considerable quantities of aluminum compounds) as to indicate strongly that decided effects result from injections of aluminum.

Group 2 consisted of three experiments in which rabbits 6, 21 and 25 (2.9 Kg. each) were each given an injection of sheep cells, followed

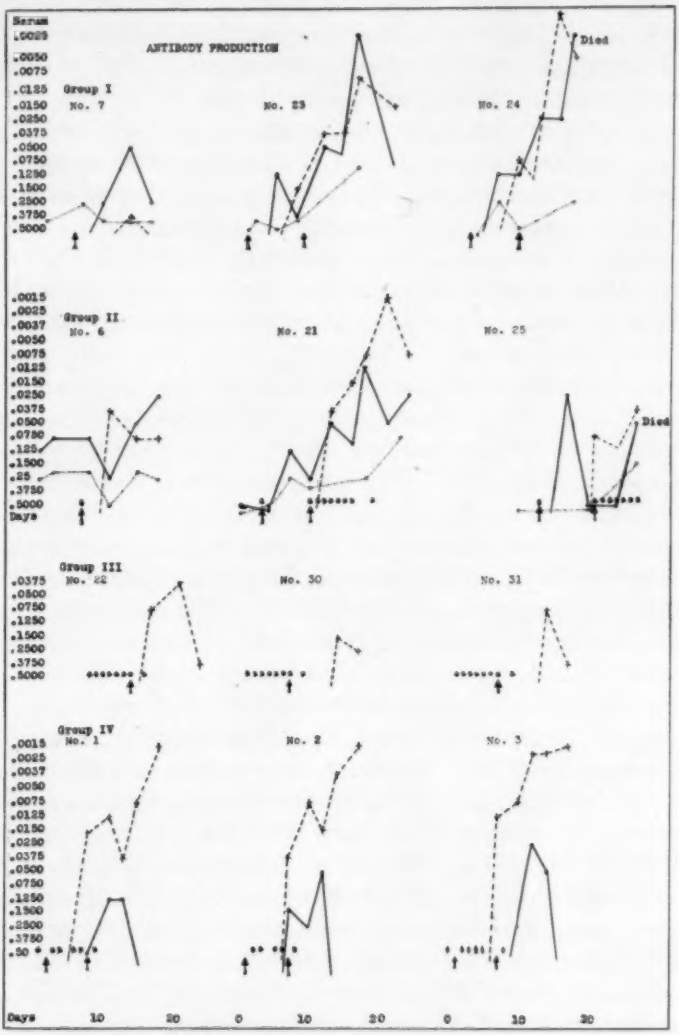

Chart 12.—The individual hemolysin, agglutinin and complement curves of rabbits treated with aluminum. The solid line represents hemolysin, the dash line agglutinin and the dotted line complement. An arrow indicates the day of injection of 5 cc. of a 50 per cent dilution of sheep cells. A star indicates the day of injection of $Al_2(SO_4)_2.Na_2SO_4.24H_2O$. A double-hilted dagger indicates the day of injection of $AlCl_3.6H_2O$.

by an injection of 0.04 Gm. of $Al_2(SO_4)_3.24H_2O$ in 5 cc. one hour afterward. Here, also, some hemolysin was produced, but little, and practically no agglutinin. Rabbits 21 and 25 were then each given a second injection of sheep cells seven days after the first injection, and then injections of alum for seven consecutive days. Rabbit 25 died immediately following the seventh injection of alum. In rabbit 21, the hemolysin rose following the second injection but never as high as in the controls; the agglutinin, however, rose high. In rabbit 25, little of either agglutinin or hemolysin was demonstrable. The remarks made concerning complement in group 1 are true also for this group.

Group 3 consisted of three experiments, in which the rabbits, no. 22 (2.7 Kg.), no. 30 (2.4 Kg.) and no. 31 (2.4 Kg.), were given injections of alum on seven consecutive days prior to the injection of the sheep cells. In all three cases, no hemolysin was demonstrable, and only a small amount of agglutinin. These results are therefore to be contrasted with the results in the control animals, in which after a single injection of sheep cells there was a small production of hemolysin, but practically no demonstrable agglutinin.

Group 4 consisted of three experiments in which rabbits 1, 2 and 3, which were showing a definite picture of anemia following extended injections of aluminum solutions (charts 1 and 4), were tested for production of antibodies. Rabbit 1, which had received forty-four previous injections of alum, was given an injection of sheep cells, then four more injections of alum, and a second injection of sheep cells six days after the first, as indicated on the chart. Rabbit 2, which had received thirty-two previous injections of alum, was treated similarly. Rabbit 3, which had received forty previous injections of $AlCl_3.6H_2O$, was also treated like nos. 1 and 2. All three showed marked production of agglutinin after the first injection of sheep cells, but no demonstrable hemolysin. Following the second injection of sheep cells, in all three rabbits, hemolysin appeared for only a short period, but the agglutinins were markedly increased. During the determinations of agglutinin, it was noted that there was a peculiar heavy precipitate in the tubes. This opens the question whether, in view of the lack of formation of hemolysin, the apparent increase in agglutinin might not really be added evidence concerning the poisoned condition of the blood, rather than a true formation of antibodies. It had been previously shown that during the poisoning of the blood with aluminum compounds the corpuscles became more resistant to hemolysis by saponin and hypotonic salt. Therefore, it seems possible that an increase in aluminum in the serum, due to injection of the aluminum compounds, prevents hemolysis of the sheep cells used in the test and at the same time causes marked agglutination of these same cells, thus giving the appearance of an increased formation of agglutinin.

COMMENT

From the results obtained in the experiments in which aluminum compounds were injected directly into the blood stream of rabbits, we conclude that the aluminum ion, introduced either combined as the sodium sulphate salt or as the chloride, produces a marked anemia, and when the dose is large enough, even causes death.

When daily intravenous injections of these two compounds were given, a definite secondary anemia was produced, i.e., there was a decrease in the percentage of the hemoglobin and in the number of the erythrocytes, an increase in the number of the leukocytes, chiefly the mononuclears, and an increased resistance of the corpuscles to hemolysis by hypotonic salt and saponin. Such increased resistance of the blood cells to hemolytic agents has been linked in lead poisoning with an increase in fragility of the corpuscles and denotes an injury to the cells. The final blood picture is also morphologically similar to that found in the later stages of lead poisoning, there being present normoblasts, poikilocytes, anisocytes, chromatophilic cells in considerable numbers and a few stippled cells.

Moreover, local irritant effects appear at the site of the injection—swelling, edema, inflammation and necrosis of the tissue and swelling of the neighboring lymph glands. All these symptoms were somewhat more marked in rabbits receiving injections of sodium aluminum sulphate than in those receiving injections of aluminum chloride.

These results are not wholly due to acid, since no similar effects were produced when a sulphuric acid solution of the same p_H as the solution of sodium aluminum sulphate was injected. A decrease in the number of erythrocytes, however, occurred when a sulphuric acid solution of p_H 2.6 was injected daily. This acidity corresponds to the maximal acidity that could be released from the alum compound, but it is improbable that a release of so much acid from alum would ever occur suddenly enough and at one time in the blood stream to give rise to the same effect as is produced by the injection of a solution of p_H 2.6.

A study of the minimal lethal dose emphasizes the toxicity of aluminum compounds. Rabbits seemed to be able to tolerate daily intravenous doses of from 0.011 to 0.017 Gm. of sodium aluminum sulphate in 0.8 per cent concentration, per kilogram, and from 0.003 to 0.004 Gm. of aluminum chloride, per kilogram, for as long as forty days, or a total of 1.5 Gm., or of from 0.416 to 0.625 Gm. per kilogram, of the former salt, before they showed visible signs of decline to such an extent that it seemed inadvisable to continue the injections without an interval of rest. However, as small a single dose as 0.25 Gm., when given in a solution of 2.5 per cent concentration, killed a rabbit weighing 1.8 Kg. immediately. This same amount (0.25 Gm.) was nonlethal when given at one time in a large volume of solution or in the concentra-

tion of 0.8 per cent to another rabbit of the same size. When 0.73 Gm. was given to this rabbit over a period of four days, death did not occur immediately, but the rabbit rapidly weakened and died twenty-four days later. A third rabbit of the same size died after receiving 0.76 Gm. over a period of seventeen days. Therefore, although a total as high as 1.5 Gm. or from 0.416 to 0.625 Gm. per kilogram of sodium aluminum sulphate could be tolerated, if given over a period of forty days, one-half that amount was lethal if given in a shorter time in the same concentration, and one sixth as much was lethal if given at one time in greater concentration.

A study of the tissues of all these rabbits revealed many lesions; namely, focal necrosis, infiltration with round cells and vacuolization of the liver cells; pigmentation, fibrosis, thrombosis and necrosis of the spleen; vacuolization of the renal epithelium and granular degeneration, necrosis and spontaneous nephritis in the kidney; lytic changes in the heart muscle cells; petechiae and ulcers in the stomach and intestines, etc. Except for the intestinal and splenic lesions, none of these lesions was found consistently in the alum-treated rabbits alone, and therefore they cannot be considered exclusively the result of treatment with aluminum compounds. It is significant that both rabbits killed by the intravenous injection of 0.73 and 0.76 Gm. of sodium aluminum sulphate over periods of from four to seventeen days showed extensive necrosis in the splenic pulp, while this never was seen in any of the control rabbits or in those that were fed alum. Similar lesions of varying degree were found in the spleens of several other animals that received aluminum, but not in the controls. Apparently, they resulted from injury to the blood, with formation of agglutination thrombi in the spleen sinuses.

These experiments leave no doubt that aluminum compounds are toxic and even lethal when put directly in contact with the blood and the tissues. There was still the question whether similar results can occur from feeding or whether the aluminum as usually ingested, i.e., in the residues of baking powder, may not be in such an insoluble form that it cannot be absorbed and therefore cannot produce these toxic symptoms.

Two sets of feeding experiments were undertaken in order to determine this point. In the first series, small daily doses of sodium aluminum sulphate (0.1 Gm. as $Al_2[SO_4]_3.Na_2SO_4.24H_20$, which is the equivalent of from 0.0007 to 0.0011 Gm. aluminum per kilogram per day) were fed to rabbits weighing from 2.5 to 4 Kg. In these experiments, extending over varying periods of time up to one year, no outward clinical symptoms were detectable, but there was an undoubted moderate decrease in the percentage of hemoglobin in most of the rabbits. No such decrease occurred in the control rabbits. Moreover,

in contrast with the unexplainable increase in the number of erythrocytes in the control rabbits fed only lactose, there were marked decreases, at times, in the number of erythrocytes of the rabbits fed the aluminum compound.

That dramatic effects, such as follow intravenous administration, cannot be expected to result from feeding the same compound is illustrated by the experiments of Sollman [15] with $Pb(Co_3)_2$. Daily feeding of $Pb(CO_3)_2$ (0.15 Gm. per kilogram or 0.11 Gm. Pb per kilogram) to rats produced no effect in thirty-five weeks, except loss of appetite and checking of growth. And yet no one doubts the harmfulness of lead as an article of food.

Aluminum is particularly toxic to red corpuscles, and it may well be that, in analogy with chronic lead poisoning, years of slow absorption of minute amounts of aluminum are required to effect the same results that are accomplished in a short time by introducing the substance directly into the blood stream. That this is a possibility is suggested by the slight changes noted in the blood after prolonged feeding of small doses of an aluminum compound.

The strongest evidence, however, that the feeding of aluminum compounds, in any form, including that supposed to be so insoluble and inert ($Al[OH]_3$) may be harmful, lies in the results obtained in the second series of feeding experiments with large single doses of aluminum compounds. Quick responses, such as decreases of from 2,000,000 to 3,000,000 in the number of erythrocytes and of as much as 20 per cent in the hemoglobin were noted in a day or two following the ingestion of large doses of aluminum, in the form of $Al(Cl_3.6H_2O)$, $Al(C_2H_3O_2)_3$, metallic aluminum, $Al(OH)_3$ (soluble gelatinous form) and $Al(OH)_3$ (granular insoluble form).

Death followed immediately after the ingestion of $Al(Cl_3.6H_2O)$ in two rabbits (1.5 Gm. equaling 0.16 Gm. metallic aluminum, in a rabbit weighing 1.5 Kg. and 10 Gm., equaling 1.3 Gm. metallic aluminum, in a rabbit weighing 3 Kg.). One rabbit died during the night following a feeding of insoluble $Al(OH)_3$ (4.25 Gm., equalling 1.47 Gm. metallic aluminum in a rabbit weighing 2.7 Kg.). The other rabbits either died three, four or more days after the feedings or were killed at the end of a month.

At autopsy, these rabbits showed chiefly toxic effects in the kidneys, such as marked swelling of the tubular epithelial cells, in one with fusion of the cells into solid, structureless, granular masses resembling casts, with loss of nuclear staining. Thrombi from agglutination were especially prevalent in the lungs, liver and kidneys in some of the rabbits, and attention is called to the apparent relationship between this

15. Sollman, T.: J. Pharmacol. & Exper. Therap. **19**:375, 1922.

phenomenon and the hemagglutinative effect of aluminum. Fatty degeneration was found in the liver, kidneys and heart in most of them. Such changes were not seen in any of the control rabbits or in those fed smaller doses of aluminum.

That these lesions, as well as the marked and sudden although transient anemias, are due primarily to the toxicity of the absorbed aluminum ion, rather than to any acid radical attached, is evident from the fact that effects follow the ingestion of the neutral $Al(OH)_3$ compounds and the metallic aluminum itself similar to those that follow the intake of acid compounds in the form of the chloride and the sulphate. There would seem, therefore, to be no doubt concerning the possibility of the absorption of aluminum following the ingestion of aluminum compounds, even when in the form of the supposedly insoluble $Al(OH)_3$, since blood changes occur similar to those following the direct introduction of aluminum into the blood stream.

A brief preliminary study of the effect of aluminum on the immunologic defenses of the body indicated that in rabbits which were showing definite symptoms of anemia and intoxication, due to extensive intravenous injections of either sodium aluminum sulphate or aluminum chloride, two injections of sheep cells failed to increase the hemolysin, whereas the agglutinative power of the serum seemed to be greatly increased, in contrast with that of the controls. As mentioned previously, these effects may be added evidence of poisoning of the blood, rather than of a change in the production of antibodies. The experiments on this phase of the problem are scanty and are reported only because of the appearance of a distinct effect due to intoxication with aluminum and as a suggestion for further work.

SUMMARY

Daily intravenous injections into rabbits of from 0.011 to 0.017 Gm. sodium aluminum sulphate per kilogram in 0.8 per cent concentration, or of from 0.003 to 0.004 Gm. aluminum chloride per kilogram in 0.2 per cent concentration, caused a very definite secondary anemia, i.e., a decrease in the percentage of hemoglobin and in the number of erythrocytes, an increase in the number of leukocytes, chiefly the mononuclears, and an increased resistance of the corpuscles to hemolysis by hypotonic salt or saponin. The final blood picture showed normoblasts, poikilocytes, anisocytes, chromatophilic cells and stipple cells. Moreover, at the site of the injection, local irritant effects appeared, such as swelling, edema, inflammation and necrosis of the tissue and swelling of neighboring lymph nodes.

Daily intravenous injections of a sulphuric acid solution, the p_H of which was the same as that of the aluminum solution (3.4) produced no similar effects. An acid solution of an acidity equivalent to the

maximal acidity that could be, but probably would not be, released from the sodium aluminum sulphate solution at any one time (p_H 2.6) produced a decrease in the number of erythrocytes, and in one rabbit caused marked local irritation at the site of the injection. But a comparison of the results obtained with the aluminum solutions and the corresponding acid solutions makes it probable that the changes so marked in the rabbits treated with the former were due chiefly to the aluminum ion.

The lethal intravenous dose of sodium aluminum sulphate seemed to vary inversely with the period of time over which it was given and also with the concentration in which it was given. Rabbits were able to survive from 0.416 to 0.625 Gm. per kilogram in a 0.8 per cent concentration if given over a period of forty days, whereas one half of this amount was lethal, if given in a shorter period of time in the same concentration. One sixth of the amount killed instantly if given in a 2.5 per cent concentration.

The feeding of small daily doses over extended periods of time and the feeding of large doses of aluminum compounds produced changes in the blood and the tissues which indicate that aluminum is absorbed through the intestinal tract and then exerts the same toxic effects as follow intravenous injection.

Rabbits daily fed sodium aluminum sulphate, mixed with lactose, in amounts of from 0.0007 to 0.0011 Gm. per kilogram for periods varying from 60 to 350 days, showed a greater decrease in the percentage of hemoglobin, than did the control rabbits. The number of erythrocytes occasionally decreased considerably. In a few rabbits there was a slight increase, but less than in control rabbits fed only lactose for the same length of time.

Rabbits fed at varying intervals with large single doses of $AlCl_3$, $Al(C_2H_3O_2)_3$, metallic aluminum, $Al(OH)_3$ in soluble form and $Al(OH)_3$ in insoluble form all showed marked sudden drops in the number of erythrocytes (of 2,000,000 or 3,000,000) and in the percentage of hemoglobin (of as much as 20 per cent). The rebound, also, in most cases, was quick. Polychromasia and slight anisocytosis and poikilocytosis were found in some.

Two rabbits were killed by a feeding of $AlCl_3.6H_2O$ (1 and 3.3 Gm. per kilogram) and one rabbit by a feeding of the insoluble form of $Al(OH)_3$ (1.58 Gm. per kilogram), and the pathologic changes in the kidneys, spleen (in one case), lungs and spinal cord (one case) were marked. The lesions in the kidneys resembled those of a selective toxic necrosis and the agglutination thrombi in the lungs, liver and kidneys indicate the absorption into the blood stream of the hemagglutinative agent—aluminum. Profound fatty degeneration was found in the kidneys, liver, and heart in two rabbits fed large amounts of $Al(C_2H_3O_2)_3$ (30 Gm.) and $Al(OH)_3$ (4.05 Gm.), respectively.

In some of the rabbits treated intravenously and fed small doses of alum over extended periods, numerous pathologic lesions were found, but only the occasional lesions of the stomach or the marked changes in the spleen, namely, thrombosis, necrosis, pigmentation and fibrosis, can be considered as primarily due to the treatment with aluminum solutions, since the other lesions were often found in control rabbits, especially those with intercurrent infections. The changes in the spleen were marked and of a character indicating the presence of a poison causing damage to the red corpuscles with agglutination and hemolysis.

A few experiments on the effect of aluminum on immunologic defenses indicated that repeated intravenous injection of aluminum, to a degree leading to definite anemia, apparently reduced the capacity of the rabbits to produce hemolysin. However, the blood of these animals showed a heightened agglutinative effect, and this contradictory result raises the question whether both the heightened agglutination and the apparent lack of hemolysin may not have depended on the effect of the alum in the serum on the tested corpuscles.

LEUKOCYTE CONTENT OF REGIONAL LYMPHATICS IN INFLAMMATION*

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Comparatively few studies have been made of the cells circulating in the lymph. In these investigations the thoracic duct or the large lymphatic vessels of the neck have usually been used as the source of lymph. This represents the ultimate collection of lymph from various parts of the body. Davis and Carlson [1] found that thoracic lymph in the dog contains from 1,000 to 30,000 cells per cubic millimeter. Kindwall [2] obtained lymph from a point situated near the junction of the external jugular and subclavian veins, which is also the point of confluence of the thoracic duct and the lymph vessels of the neck. He reported that the cells of the lymph of the rabbit are practically all lymphocytes; monocytes were rarely found. He therefore concluded that monocytes are not produced by lymphopoietic tissues, but when found are only chance invaders of the lymph stream. Forkner,[3] on the other hand, recently reported that monocytes are normal constituents of all the lymph nodes of the rabbit, except the mesenteric mass. He agreed, however, that monocytes are not normally present in efferent lymphatic vessels.

A few years ago Opie [4] pointed out that "the local changes which with inflammation occur in the lymphatic vessels of the affected part and in the tributary lymphatic nodes are not separable from the changes which have their seat in the blood vessels and in the interstitial tissue." Within forty-five minutes after the injection of *Staphylococcus aureus*

* Submitted for publication, May 1, 1929.

* From the Henry Phipps Institute, University of Pennsylvania.

1. Davis, B. F., and Carlson, A. J.: Contribution to the Physiology of Lymph: IX. Notes on the Leukocytes in the Neck Lymph, Thoracic Lymph and Blood of Normal Dogs, Am. J. Physiol. **25**:172, 1909-1910.

2. Kindwall, J. A.: A Supra-Vital Study of the Cells in the Lymph Stream of the Rabbit, Bull. Johns Hopkins Hosp. **40**:39, 1927.

3. Forkner, C. E.: Material from Lymph Nodes: IV. The Heterology of Lymphoid Tissue with Special Reference to the Monocyte-Supravital Studies, J. Exper. Med. **49**:323, 1929.

4. Opie, E. L.: Inflammation, Arch. Int. Med. **5**:541 (June) 1910.

into the subcutaneous tissue of the leg of a guinea-pig, Bezançon and Labbé [5] found that the afferent lymphatic vessels were dilated and contained many polymorphonuclear cells.

The object of the present investigation was to study the leukocyte content of lymphatic vessels draining a relatively small area into which a sterile inflammatory irritant had been previously injected.

METHOD

The experimental procedure employed was as follows: 3 cc. of a sterile inflammatory irritant was injected subcutaneously into the extensor surface of one of the forelegs of a rabbit, about 2 or 3 cm. from the shoulder joint. The irritant used was either infusion broth containing neither salts nor peptone and concentrated to one tenth of its original volume [6] or else a 0.5 per cent saline solution containing 5 per cent aleuronat and 3 per cent starch.

After varying periods ranging from eighteen to forty-eight hours, the animal was anesthetized with ether. The lymph was obtained by a method recently devised by Freund and Whitney, and adequately described by these authors elsewhere.[7] In brief, the method was as follows: The skin was incised below and parallel to the clavicle. The pectoral muscles were severed and the subclavian vein was exposed. Alongside of this vein and crossing it, usually at its distal end, an efferent lymphatic vessel was seen. Cannulation was performed by means of a capillary pipet. At its distal end and slightly below the subclavian vein, the efferent vessel connects with an axillary lymph node in which two or three small afferent lymph vessels may be seen to terminate. The afferent channels could also occasionally be cannulated. The leukocyte picture in the lymphatic vessel of the opposite side of the animal was often used as a normal control over the observations on the inflammatory side.

To prove that the channels studied were the tributary lymphatics and were therefore draining the area of inflammation, a 1 per cent trypan blue solution in physiologic solution of sodium chloride was injected subcutaneously at the site where the inflammatory irritant was usually injected. From twenty to thirty minutes later the regional lymphatic vessels and lymph node displayed the dye prominently.

The leukocytes were studied by the supravital technic as described by Sabin.[8] Neutral red was the only dye used. The basophils, eosinophils and neutrophils were all grouped together as polymorphonuclears. The monocytes were distinguished from the clasmatocytes by the "rosette" formation. To obtain the differential formula usually 200 cells were counted. In several experiments, histologic sections were also made of the inflamed area and of the regional lymph node.

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5. Bezançon and Labbé: Arch. de méd. expér. **10**:318, 1898; quoted by Opie (footnote 4).

6. Gay, F. P., and Morrison, L. F.: Clasmatocytes and Resistance to Streptococcus Infection, J. Infect. Dis. **33**:338, 1923.

7. Freund, J., and Whitney, C. E.: Distribution of Antibodies in the Serum and Organs of Rabbits: III. Agglutinin Content of the Lymph and Tissue of the Liver and of the Lymph and Muscle of the Leg, J. Immunol. **16**:109, 1929.

8. Sabin, F. R.: Studies of Living Human Blood-Cells, Bull. Johns Hopkins Hosp. **34**:277, 1923.

RESULTS

In several normal rabbits, the efferent lymphatic vessel was cannulated and its cellular content was studied. Table 1 shows that in the normal efferent lymphatic vessel, the cells were practically all of the lymphocyte type. Only rarely an occasional monocyte was found. It

TABLE 1.—*The Leukocyte Picture in an Efferent Lymphatic Vessel in Normal Rabbits*

Rabbit	Absolute Number of Leukocytes per Cu. Mm.	Percentage of Polymorphonuclears	Percentage of Lymphocytes	Percentage of Monocytes	Percentage of Clasmatocytes
1	11,300	0	100.0	0.0	0
2	55,000	0	100.0	0.0	0
3	15,000	0	100.0	0.0	0
4	9,000	0	100.0	0.0	0
5	24,000	0	100.0	0.0	0
6	14,400	.	.....	...	.
7	12,000	.	.....	...	.
8	.....	0	99.5	0.5	0
9	.....	0	100.0	0.0	0
10	17,500	0	99.5	0.5	0
11	14,000	0	100.0	0.0	0
12	.....	0	100.0	0.0	0

TABLE 2.—*The Leukocyte Picture in an Efferent Lymphatic Vessel in the Region of Local Inflammation*

Inflammatory Irritant	Rabbit	Hours After Injection of Irritant	Absolute Number of Leukocytes per Cu. Mm.	Percentage of Polymorphonuclears	Percentage of Lymphocytes	Percentage of Monocytes	Percentage of Clasmatocytes
Infusion broth (concentrated)	14	18	17,000	15.5	83.0	0.0	1.5
	12	18	.....	8.0	90.0	0.5	1.5
	9	19	.....	1.5	98.0	0.5	0.0
	10	20	.....	11.5	79.5	2.5	6.5
	8	22	.....	5.0	92.0	2.0	1.0
	11	23	.....	14.0	85.0	1.0	0.0
	15	46	.....	4.5	95.5	0.0	0.0
	13	48	6,200	6.5	90.5	1.5	1.5
Aleuronat	24	17	34,200	3.5	92.0	4.0	0.0
	20	18	.....	33.0	66.3	0.6	0.0
	27	18	10,000	16.0	83.5	0.5	0.0
	22	20	20,000	20.0	79.0	1.0	0.0
	17	21	5,750	3.3	96.6	0.0	0.0
	25	21	25,000	6.0	94.0	0.0	0
	23	21	25,700	7.5	92.5	0.0	0
	16	22	48,000	74.0	24.3	0.3	1.3
	21	23	24,750	17.0	83.0	0.0	0
	18	24	.....	36.3	63.2	0.5	0
	26	28	15,600	2.5	97.5	0.0	0
	19	49	.....	1.0	99.0	0.0	0

is noteworthy that this agreed with the observations of previous investigators, who examined lymph from other vessels. The absolute counts varied greatly, ranging from 9,000 to 55,000 leukocytes per cubic millimeter.

Table 2 reveals the leukocyte picture in an efferent regional lymphatic vessel as a response to a local inflammatory process. There was a definite qualitative change in the differential formula. Whereas normally polymorphonuclear cells were not found in the efferent lymphatic

vessel, a local inflammation caused by a sterile irritant revealed in each case the presence of polymorphonuclears. The percentage of these cells varied widely, ranging anywhere from 1 to 74 per cent. The significant point, however, was that the polymorphonuclear cells could always be found in the efferent lymph vessel when an inflammatory irritant had been previously injected. Other types of cells were not found so constantly, although, when the observations here were compared with the observations in normal animals, there seemed to be in some of the rabbits receiving the injections a tendency toward a slight increase in monocytes and clasmatocytes. The absolute numbers of leukocytes per cubic millimeter were too variable to permit any definite inference as to their possible significance.

COMMENT

This study clearly brings out the fact that a local inflammatory process produces a change in the differential leukocyte formula of a regional efferent lymphatic vessel. Polymorphonuclears, in varying proportions, always appear. Histologic sections of both the site of injection and the regional lymph node reveal an inflammatory process, showing that the inflammation extends at least as far as the regional lymph node. The presence of polymorphonuclear cells in the efferent lymphatic vessel indicates that at least some of these cells are returned from the inflamed region to the blood stream through the lymphatic channels.

SUMMARY AND CONCLUSIONS

The cellular content of an efferent lymphatic vessel of one of the axillary lymph nodes of the foreleg of a normal rabbit consists almost entirely of lymphocytes.

When local inflammation is produced by a sterile irritant, polymorphonuclears appear in the efferent lymphatic vessel of the regional lymph node.

Local inflammation after from eighteen to forty-eight hours often causes the monocytes and clasmatocytes to increase in number in the efferent lymphatic vessels; but this increase is not so constant as the presence of polymorphonuclears.

The inflammatory reaction involves both the site of the injection and the regional lymph node.

The polymorphonuclear leukocytes that migrate from the blood vessels into the inflamed area return, in part, to the blood stream by way of the lymphatics.

Laboratory Methods and Technical Notes

AN IMPROVED RACK FOR STERILIZING VACCINES*

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Sterilization of bacterial suspensions by submerging the test tubes or bottles containing them in a water bath at 60 C. is the usual method in many laboratories. If the amount of bacterial suspension in the container is small, it is difficult to keep it submerged so as to have the water in the bath well above the fluid level of the vaccine suspension. The rack here described was designed to meet this requirement.

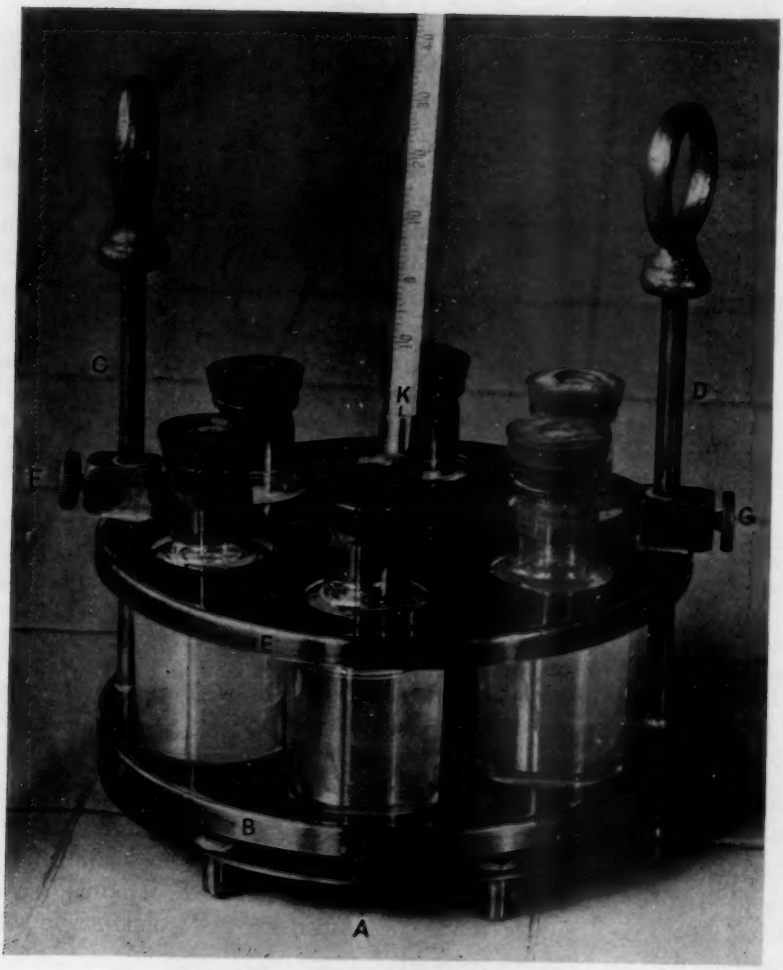
It consists of a circular, perforated, heavy metal base, *A*, mounted on legs (fig. 1). Two upright metal rods, *C* and *D*, are fixed to it. A second copper disk, *B*, with six holes, each large enough to accomodate a vaccine bottle of 30 cc. capacity, is attached at a distance 1 cm. above the disk *A*. A third movable metal disk, *E*, slides up and down on the rods *C* and *D*. It has six circular holes in it, so fashioned that each will fit over the neck of a vaccine bottle of 30 cc. capacity. Two set screws, *F* and *G*, secure the disk *E* in the position desired. There is a perforated slot, *K*, for holding a thermometer, soldered into the center of the disk *E*. The largest diameter of the rack is 13 cm. and its height is 16 cm.

The bacterial suspension is placed in a vaccine bottle of 30 cc. capacity and this is stoppered with a sterile rubber cap. The disk *E* is brought down securely over the neck of the bottle and fixed in position by means of the set screws *F* and *G*. A thermometer is inserted into the slot *K*, and the apparatus is placed in the water bath; the level of the water reaching up to the neck of the vaccine bottle, beyond the lower level of the rubber cap.

The rack is of simple construction. Any skilled coppersmith can build one. It is small enough that even the inner boiler of a rice cooker may be used as a satisfactory water bath. There is no floating up of the vaccine container; when placed in the water bath, it remains completely submerged and both vaccine suspension and container may be maintained at an even temperature.

* Submitted for publication, April 19, 1929.

* From the Pathological Laboratories, Jefferson Medical College Hospital.



A rack for sterilizing bacterial suspensions.

THE CELL-PLASMA RATIO*

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It has long been recognized that marked variation occurs in the plasma content of the blood relative to its cell content both in health and in disease. In health, the most important factor in the variation is the ingestion of large quantities of fluid. In disease, the prime factor is hydremia associated with primary renal disease or circulatory failure or some condition in the tissues of the body involving the chemistry of colloids and crystalloids. Indirectly, there is a relative increase in the plasma in primary and most secondary anemias, in which the number of the red blood cells is markedly reduced.

In any type of anemia and more particularly in anemia due to hemorrhage, periodic study of the cell-plasma ratio may be of value in the differential diagnosis and as a check on the therapy. The study of the cell-plasma ratio has led, moreover, to a more precise method for the estimation of hemoglobin, as will be described in another part.

METHOD

1. Shake a few grains of dry powdered sodium citrate into a clean, dry capillary glass tube having an inside diameter of 4 mm. and a length of 10 cm.[1]

2. Holding the tube in the horizontal position or with the distal end slightly depressed, apply the proximal end to a bleeding puncture wound. A rapid, deep, incised wound of the finger made with a sharp lancet-headed needle will fill at least three such tubes with little or no pressure on the finger.

3. Fill the tube about two-thirds full, and mix the blood with the citrate by alternately elevating and depressing one end.

4. Allow the blood to gravitate to one end, seal that end with a plug of paraffin and place a broad rubber band snugly around the length of the tube, thus sealing both ends. It is well to file off the cut edges to avoid injury to the finger or tearing of the rubber band.

5. Centrifugate at high speed (plugged end down) for a sufficient length of time to secure the maximal separation of cells and plasma. This is determined as the length of time after which repeated centrifugation no longer diminishes the length of the cell column. Once established, the same button on the rheostat and the same period of time may be used with every specimen.

6. Measure the cell column and the plasma column with a millimeter rule, and determine the percentage of each (e. g., 30 mm. of plasma and 30 mm. of cells are equivalent to plasma 50 per cent and cells 50 per cent or a cell-plasma ratio of $\left(\frac{c}{p}\right)$ 1).

Method Using Venous Blood Compared with Method Using Capillary Blood.—Contrary to expectations, it was found that little difference obtained in the results

* Submitted for publication, April 26, 1929.

* From the Laboratory of St. Bartholomew's Hospital.

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whether capillary or venous blood was used. Even prolonged and marked pressure on a bleeding digit elicited only a slight error. Prolonged application of a tourniquet, however, made a small but definite error in the case of venous blood.

Method Using Capillary Tube as Container Compared with Method Using Centrifuge Tube.—A check was then made against the 15 cc. graduated centrifuge tube. It was found that the thickness of the column of blood in the centrifuge tube increased the inaccuracy of the reading many times as compared with the slender column in a capillary tube. With the exercise of great care, however, the readings were comparable. Thus, repeated reading in a case of polycythemia vera gave plasma 31 per cent and cells 69 per cent for the capillary tube and plasma 40 per cent and cells 60 per cent for the centrifuge tube.

APPLICATION OF METHOD

As it had been determined in a series of 500 cases that in the hands of different technicians the cell plasma values of venous and of capillary blood were comparable, capillary blood alone was used, except in isolated instances.

Variations in the Normal Person.—It was found that in the normal person great variation occurred in the proportion of plasma to cells. This was most marked within the first half hour after ingestion of large amounts of fluid, the relative plasma value then being high, and in starvation, the relative plasma value then being low. The influence of fluids was so marked that one could almost trace the rate of the water-absorption by periodic determinations of the cell-plasma ratio. Constant values in any one person were found under basal conditions (fourteen hours' fast and rest in bed). The average value of the plasma in the blood from a healthy man or woman under basal conditions was from 45 to 55 per cent and the average value of the cell-plasma ratio was 1 or a little less than 1. That is, the plasma column was nearly always slightly longer than the cell column. The value of the cell-plasma ratio $\left(\frac{c}{p}\right)$ was obtained by dividing the percentage of cells in the column of centrifugated blood by the percentage of plasma. Excessive sweating and exercise tended to increase the ratio in almost direct proportion to their intensity and duration.

Variations in Persons Presenting Pathologic Conditions.—Severe secondary types of anemia, especially those associated with hemorrhage (e. g., duodenal ulcer), primary anemias, severe diabetes and nephritis with water retention show a relative increase in plasma content and, therefore, a cell-plasma ratio of much less than 1. In cases of bleeding gastric or duodenal ulcer, the ratio is lowest within the primary post-hemorrhagic period when the vessels are being rapidly filled with fluid. The ratio slowly rises, approaching 1 as the cells are regenerated. It is a more reliable index of the progress of a bleeding lesion than the percentage of hemoglobin and the blood count. Persistent loss of blood is accompanied by a low ratio, which is proportionate in a measure to

the duration and severity of the hemorrhage. Table 1, showing the determinations of the cell-plasma ratio in a case of bleeding gastric ulcer, illustrates this point. Autopsy disclosed extensive ulcerations of the prepyloric region with evidence of a recently plugged vessel of moderate size in the floor of one ulcer. The wall of this ulcer also showed early carcinomatous changes.

TABLE 1.—*Comparison of the Percentage of Hemoglobin and Number of Red Cells with the Cell-Plasma Ratio in a Case of Hemorrhage from Duodenal Ulcers*

Date	Hemoglobin, per Cent	Red Cell Count	Cell-Plasma Ratio	Remarks
8/ 8/28	74	3,850,000	0.31	
8/10/28	..	.....	0.50	96 hours after hemorrhage
8/11/28	60	.....	0.40	
8/13/28	58	3,200,000	0.30	Hemorrhage
8/14/28	..	.....	0.15	
8/28/28	50	3,680,000	0.42	
9/ 4/28	50	3,000,000	0.26	
9/11/28	..	.....	0.50	1 hour before death

TABLE 2.—*Effect of a Blood Transfusion on the Cell-Plasma Ratio in a Case of Hemorrhage from Duodenal Ulcers*

Date	Cell-Plasma Ratio	Remarks
8/16/28	0.30	A few minutes before a transfusion of 1,000 cc. of blood (direct method)
8/16/28	0.20	Five minutes after the transfusion
8/17/28	0.31	Twenty-four hours after the transfusion
8/18/28	0.26	Forty-eight hours after the transfusion

TABLE 3.—*Comparison of the Percentage of Hemoglobin and Number of Red Cells with the Cell-Plasma Ratio in a Case of Duodenal Ulcer*

Date	Hemoglobin, per Cent	Red Cell Count	Cell-Plasma Ratio	Remarks
10/ 3/28	80	5,240,000	0.75	Before dinner
10/ 6/28	80	4,410,000	0.85	Before dinner
10/ 7/28	..	.....	0.26	Gastro-enterostomy 1 hour after hypodermoclysis and 5 minutes before a transfusion (1,000 cc. by direct method)
10/ 7/28	..	.....	1.2	Ten minutes after the transfusion
10/16/28	..	.....	1.5	
10/16/28	..	.....	1.0	Taken shortly after dinner
3/11/29	72	4,000,000	0.39	Taken before breakfast

A transfusion in the same case is interesting in that it caused no considerable change in the ratio for at least forty-eight hours (table 2).

Another patient studied over a longer period showed somewhat different results (table 3). This patient was a woman of the thin, scrawny, dehydrated type, who had a duodenal ulcer. The high values of the cell-plasma ratio in this case were probably associated with dehydration, which was possibly due to the short circuiting of the gastric contents.

At the time of the last estimation, the patient had returned to the hospital because of an adherent gallbladder which had perforated and ruptured into the stomach. The transfusion in this case had changed the proportion from cells 21 per cent and plasma 79 per cent to cells 58 per cent and plasma 42 per cent. It suggests the rapidity with which fluids may pass from within blood vessels to dehydrated tissues.

The healthy donor who had been used for the transfusion showed no change in the cell-plasma ratio. This was probably due to the rapidity of the withdrawal of blood, and indicates that in the loss of blood by mechanical means without associated shock it takes some time for the body fluids to attempt to make up the loss of fluid. Clinically, the average healthy donor rarely experiences thirst after a transfusion of moderate size. It is not at all unlikely that in a robust person such a transfusion causes little disturbance in the fluid balance.

In marasmus, cachexia and all other states associated with dehydration, the cell-plasma ratio is high owing to the relative concentration of the cellular elements.

In chlorosis and polycythemia there is an absolute increase in the number of erythrocytes and a resulting high cell-plasma ratio. This is illustrated in a case of polycythemia in which the percentage of the hemoglobin was 110, the number of the red cells 7,040,000 and the cell-plasma ratio 1.5.

SUMMARY

The cell-plasma ratio affords a simple index to the relative concentration of cells and plasma in the blood.

Some normal and pathologic variations have been described.

The practical application of this method in the study of hemorrhagic states has been illustrated.

General Review

RECENT WORK ON THE EFFECTS OF INANITION AND MALNUTRITION ON GROWTH AND STRUCTURE

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MINNEAPOLIS

(Concluded from page 1078)

Effects of a Deficiency of Vitamin E. (Antisterility).—The existence of a fat-soluble antisterility vitamin E may be regarded as definitely established through the pioneer work of Evans and his associates, confirmed by Sure (1924, 1926, 1926a, 1926b), Mattill and his associates (1924, 1926, 1927), Daniels and Hutton (1925), Mason (1925, 1926), Beard (1926), Kennedy (1926), Tso (1927) and Suzuki and his co-workers (1928). Some skepticism, however, has been expressed, especially by Hogan and Harshaw (1924), Nelson and his associates (1926) and Hartwell (1926). In reviewing the question, Kennedy (1926a) concluded that "as yet it has hardly emerged from controversy, but it is impossible to deny that the evidence in its favor is very strong."

The earlier papers by Evans and Bishop, announcing the discovery of the antisterility vitamin, were reviewed in my previous work (Jackson, 1925). Evans and Burr (1925), Evans (1925) and Evans, Burr and Althausen (1927) presented more detailed evidence that rats reared on various synthetic mixtures of protein, fat, carbohydrate, salts and vitamins (A, B and D) grow well but exhibit sterility unless the diet is supplemented by vitamin E. According to Beard (1926), a similar factor is apparently necessary for normal reproduction in the mouse. A possible relationship between the antisterility vitamin E and the assimilation of iron was suggested by Hart and his co-workers (1925) and Simmonds, Becker and McCollum (1927). Recently (1928), however, the latter authors withdrew this suggestion. The character of the sterility is different in the two sexes, which must therefore be considered separately. Evans (1928b) recently showed that the maximum body weight attained is distinctly higher in rats of both sexes when vitamin E is adequately supplied. Bisceglie (1928) found that deficiency of vitamin E in rats results in histologic changes (interpreted as hyperfunctional) in the thyroid, suprarenal and hypophysis.

Reproduction in the Male (Sterility): While the earlier investigation was devoted chiefly to the effects in the female rats, Evans and Bishop (*J. A. M. A.* **81:** 889, 1923) noted that the spermatozoa also

are injured and eventually destroyed by the deficiency of vitamin E. Mattill and associates (1924, 1926) observed that in male rats, over 100 days old, on diets deficient in vitamin E, there is a decline in procreative power, associated with progressive degeneration of the testis. In advanced stages, the testis is from 40 to 70 per cent subnormal in weight. The sperm cells and the lumen of the seminiferous tubules disappear, but the interstitial tissue proliferates. After the animals are 5 months of age, the recovery of the degenerated testis on the administration of vitamin E is rarely possible.

The histologic effects of a deficiency of vitamin E on the testis of the rat were studied in detail by Mason (1925, 1926). After the rats had been from three to five months on a diet deficient in vitamin E (beginning at weaning), the weights of the testes averaged only 44 per cent of normal. Degeneration began in from fifty to sixty-five days, and was practically complete after 100 days. The stages of degeneration in the seminiferous tubules were: (1) clumping of the spermatozoa, which became detached in irregular masses; (2) disappearance of the spermatozoa in most tubules, and karyorrhexis of the spermatids, with disappearance of the cell walls; (3) formation of multinucleated giant cells by fusion of the degenerated spermatids, with a beginning degeneration also in the spermatocytes; (4) presence of a few remaining giant cells, with the spermatocytes and the spermatogonia in various stages of necrosis; (5) reduction of the germinal epithelium to a syncytial layer of Sertoli's cells in the periphery of the shrunken tubules, with the interstitial cells not degenerated, and the epithelium in the ducts of the epididymis showing fatty degeneration in extreme cases.

The destruction of the male germ cells, and eventually of the entire seminiferous epithelium, was also noted by Evans (1925), Evans and Burr (1925) and Suzuki and his associates (1928). The process was described fully in a recent monograph by Evans, Burr and Althausen (1927). They recognized the following stages of sterility: (1) a short period during which the spermatozoa (from the vaginal plug) appear normal in number, morphology and motility, but have already lost their fertilizing power; (2) a period similar to stage 1, but with loss of motility by the spermatozoa; (3) a period similar to stage 2, except for the appearance of isolated groups of spermatozoa, together with attached Sertoli's cells; (4) disappearance of sperm from the plug; (5) loss of power to form the plug, with preservation of some sex interest, and (6) loss of all sex interest. In late stages of sterility, with normal body weight (about 400 Gm.), the testes are only about one-third normal weight, and are pigmented and watery in structure. Histologically, the tubules show a progressive (to total or nearly complete) loss of seminiferous epithelium, as described by Mason.

While the interstitial (Leydig) cells apparently remain normal, there may be an increase in connective tissue macrophages, associated with phagocytic resorption of the degenerated seminiferous epithelium. The testes of males of the second or succeeding generations on the deficient diets degenerate earlier than those of males of the first generation. On the feeding of a curative diet containing vitamin E, recovery of the normal structure by regeneration from islands of resistant germinal epithelium is possible, but may be attained in only one fourth of the cases, even when the curative diet is fed as soon as the sterility appears. Tubules reduced to Sertoli's cells only are apparently unable to regenerate and persist unchanged.

The effects of a deficiency of vitamin E on the testis appear, in general, similar to those previously described by many investigators as occurring in various forms of partial or total inanition. In some cases, in the earlier experiments, the effects observed may have been due to an unrecognized associated deficiency of vitamin E. Mattill (1927) and Evans (1928a) presented evidence indicating that in rats a deficiency of vitamin B (which has been considered especially harmful to the testis) rarely causes testicular degeneration when vitamin E is adequately provided.

Reproduction in the Female (Sterility): It is most remarkable that while a deficiency of vitamin E causes sterility also in the female, the process is radically different from that in the male. Recent work by Mattill, Carman and Clayton (1924), Mason (1925), Evans and Burr (1925) and Suzuki and his associates (1928) strongly confirmed the original discovery by Evans and Bishop that in the female rat during a deficiency of vitamin E the ovary and ovulation, fertilization and implantation remain unimpaired, but sterility occurs through resorption of the implanted embryos. Bisceglie (1928) alone found a profound degeneration of the ovarian follicles.

The process was recently described in detail in the excellent monograph by Evans, Burr and Althausen (1927). Their extensive and carefully controlled observations revealed nothing abnormal occurring during the period of deprivation of vitamin E until the eighth day of gestation. From that time, retardation and abnormality of embryonic development became progressively evident until the death of the fetuses, about the thirteenth day, followed by rapid fetal and (later) placental resorption. The embryos showed subnormal development, which affected especially the mesodermal derivatives. The yolk sac showed a reduced size and a smaller number of entodermal villi and of mesodermal blood islands. The outgrowth and differentiation of the allantois were impaired. The maternal placenta was reduced in size but was nearly normal in structure. It continued to grow for several days after the fetal death, but was later resorbed. Early fetal death followed

subnormality of the yolk sac; later death followed injury of the allantois. The hematopoietic organs of the embryo were reduced, and the entodermal anlage of the liver was often subnormal. There was a striking reduction in the number of blood cells in the embryonic vascular system. The anemia and subnormal development of the yolk sac and allantois probably resulted in fetal death through starvation and asphyxia.

About two months were required to exhaust the stored vitamin E of female rats that previously had been on normal diet. When females were reared from weaning time on diet free from vitamin E, enough of the vitamin might be retained to permit one normal gestation (rarely more). While a lack of vitamin E caused female sterility, an excess of the vitamin did not increase either the normal number of young in a litter or the average weight at birth.

Even on normal diets, however, resorption occurred in about 7 per cent of the embryos. Barry (*Carnegie Contrib. Embryol.* no. 53, 1920) observed fetal resorption resulting also from the starvation of pregnant rats. It therefore appears doubtful whether the contention is justified that fetal resorption occurs only from the deficiency of vitamin E. In most cases, however, female malnutritional sterility is undoubtedly brought about through a suppression of ovulation rather than through a disturbance of the process of gestation.

While a deficiency of vitamin E apparently causes anemia in the embryo, Kohls and Evans (1928) did not find evidence that it produces anemia in adult rats. Bishop and Morgan (1928) observed the spontaneous occurrence of multiple deciduomas in the uterus of a rat on a diet deficient in vitamins A and E.

Lactation: Simmonds (1924) and other investigators found difficulty in rearing young rats through the nursing period when the mothers were placed on many natural or synthetic diets apparently containing all the necessary nutritional factors. Evans (1924) noted that even with the inclusion of vitamin X (E), the food requirements for lactation were not fulfilled. The question was recently discussed by Tso (1927) and Evans and Burr (1927a, 1928a). One view (now well established) is that the process of lactation requires an enormous increase in some of the known dietary factors, as was shown by Simmonds for protein and by Sure, Evans and Burr, and others for the requirement of vitamin B during this period. The other possibility is that certain natural foods contain some more specific galactagogue factor that has not yet been demonstrated.

Paralysis of the Young: As was recently shown by Evans and Burr (1928a), when mother rats are on diets deficient in vitamin E, the young appear to grow normally during the lactation period, but nearly three fourths of them develop a partial paralysis. This is frequently

noted a day or two before weaning and becomes progressively severe during the next four or five days. The musculature of the body wall is affected, so that the rats are unable to right themselves when placed on their backs. The hind limbs present a spastic paralysis, in some cases preceded by flaccid paralysis, with dragging of the limbs. About 35 per cent of the affected animals die, 17 per cent (mild cases) recover fully, and 48 per cent continue paralyzed to a variable extent throughout life. After two or three months, many develop bilateral atrophic skin lesions with bare areas over the upper part of the thigh and the mid-dorsal region. The administration of vitamin E does not cure the paralysis after it is once well established, but some of the paralyzed females have later been able to become pregnant and give birth to normal young.

Effects of a Deficiency of Recently Discovered Vitamins.—As mentioned in the section on vitamin B, much evidence has accumulated, establishing beyond reasonable doubt the composite nature of this vitamin. As early as 1915, Funk and Macallum recognized the possibility of separable growth components in yeast. Mitchell (1919) reviewed the conflicting evidence as to the identity of the water-soluble growth-promoting vitamin and the antineuritic vitamin. McCollum and his associates formerly supported the view that the water-soluble B represents a single vitamin, but most of the more recent work has tended to confirm the theory that yeast (and some other carriers of vitamin B) contain at least two separable factors: the heat-labile antineuritic (anti-beriberi) vitamin and the heat-stable "growth-promoting" vitamin. The heat-stable factor appears somewhat similar to Wildiers "bios," or Funk's "vitamin D" (not to be confused with McCollum's antirachitic vitamin D), and is probably identical with Goldberger's antipellagra ("P-P") factor. Both of the component factors of B appear necessary for health and growth, and both are usually abundant in yeast. Wheat and maize germs seem to be relatively rich in the antineuritic vitamin, but poor in the antipellagra factor.

Experimental evidence for the composite nature of vitamin B has been presented by numerous investigators, including the following (using the rat or pigeon in most cases): Emmett and Luros (1920), Funk and Dubin (1921), Heaton (1922), Levene and Muhlfeld (1923), Smith and Hendrick (1926), Goldberger, Wheeler, Lillie and Rogers (1926), Goldberger and Lillie (1926), Hauge and Carrick (1926), Goldberger (1927) in human pellagra, Salmon (1927), Salmon, Guerrant and Hays (1927), Chick and Roscoe (1927), Hassan and Drummond (1927), Sherman and Axtmayer (1927), Williams and Waterman (1927), Eddy (1927), Evans and Burr (1927a, 1928c), Kennedy and Palmer (1928), Findlay (1928), Black, Sassaman and Holaday (1928) and Hogan and Hunter (1928).

The nomenclature of the newly discovered vitamin factors is in a state of great confusion, as was recently well shown by Smith (1928). Shall the term vitamin B be abandoned (as suggested by Sherman), or retained merely in the old, composite sense (Salmon, Smith) or restricted to designate only one of the newly recognized factors? To retain the term vitamin B in the composite sense would be contrary to precedent in the case of vitamin A, which originally meant the composite fat-soluble vitamin, but was later restricted by excluding the antirachitic factor (D). The proposal of the British Committee on Accessory Food Factors to use B_1 for the thermolabile (antineuritic) factor and B_2 for the thermostabile factor is likewise open to serious objections, as noted by Smith (1928) and Dutcher (1928).

If the term vitamin B is in the future to be restricted to one of the component factors, which shall it be? Chick and Roscoe suggested vitamin B *sensu stricto* to designate the "growth promoting," or antipellagra, factor. This appears undesirable, since beriberi and polyneuritis have been so long and so prominently associated with a deficiency of vitamin B. Growth, on the contrary, is a more generalized function, dependent on more than a single vitamin; and the probable relationship of the second B factor to pellagra has been only recently recognized. It would therefore seem more logical and more satisfactory to retain the term vitamin B in the restricted sense of the antineuritic factor, in accordance with the usage of Goldberger and others, and contrary to the proposal of Sherman and Smith. This plan is supported by McCollum (Dutcher, 1928) and by Hogan and Hunter (1928).

If vitamin B is to mean the antineuritic vitamin, what term shall be adopted to designate the second B factor? The term "growth-promoting" has been frequently used for this factor, but it appears inappropriate, since both B factors (as well as other vitamins) are essential for growth. Salmon proposed "B-P" factor for the antineuritic, and "P-P" (Goldberger's pellagra-preventing) for the second factor. Sherman suggested "vitamin F" for the antineuritic factor and "vitamin G" for the growth-promoting or antipellagra factor ("P-P"). But if vitamin B is to be retained for the antineuritic factor, it seems more logical (as proposed by Hogan and Hunter) to use "vitamin F" for the second growth-promoting factor, which appears to be closely related to (if not identical with) Goldberger's pellagra-preventing ("P-P") factor. Evans and Burr (1927a, 1928b), recently suggested the term "vitamin F" to designate another growth-promoting dietary factor, to be discussed later. This factor might instead be termed "vitamin G," if the newly discovered vitamins are (as in the past) to be designated by the letters of the alphabet in approximate order of discovery.

As to the effects of a dietary deficiency of the second, growth-promoting (or antipellagra) factor, most of the investigators noted merely a failure of growth in young animals. Young rats on diets thus deficient, as a rule, soon cease to grow, and after a variable period of nearly stationary weight, usually show a progressive emaciation with a decline in weight, and die from malnutrition without any external evidence of special lesions. In certain cases, however, especially of older animals subjected to experiment for long periods, characteristic disturbances of the skin and other symptoms suggestive of pellagra have been observed.

Antipellagra Factor (P-P), B_2 or Vitamin F: Credit for the discovery of the antipellagra factor is due chiefly to Goldberger and his associates. Continued work in this field led Goldberger to abandon his former theory that pellagra is caused by a dietary deficiency of protein. "Summing up," he wrote in 1926, "it may be stated that the available evidence seems to leave no reasonable doubt but that pellagra is caused by a faulty diet. The primary dietary fault appears to be of the nature of a deficiency of a factor P-P, very probably but not certainly identical with a dietary essential heretofore included with the anti-neuritic under the designation 'vitamin B,' which some workers have attempted to identify with bios." Goldberger (1927) described the distribution of this heat-stable factor in various foodstuffs (it is especially abundant in yeast and lean meat), and concluded that in pellagra in man "this deficiency arises when the diet does not include enough of the foods which carry the vitamin P-P to supply the needs of the body for this food factor."

This factor P-P ("pellagra-preventing") was first recognized by Goldberger and Tanner (1925) in dietary experiments with pellagra in man. Further experiments on animals were reported by Goldberger and Lillie (1926). When young rats were fed a diet apparently complete except for the antipellagra factor, growth was soon arrested, but symptoms of polyneuritis did not occur even when the experiment continued far beyond the period when such symptoms appear during a deficiency of vitamin B. Many of these rats ultimately developed symptoms of ophthalmia and pellagra-like lesions of the skin. There was a variable loss of fur, usually beginning on the head, neck or shoulder. The depilation sometimes extended to an almost complete denudation of the head, neck and trunk. The denuded areas were often sharply delimited and were bilaterally symmetrical. Either with or without such loss of fur, some rats developed a dermatitis with bilaterally symmetrical lesions of the ears, the front of the neck and the chest or the limbs (paws). The shortest period within which this dermatitis appeared was about seven weeks. A few rats showed ulcerative lesions at the angles of the mouth or the tip of the tongue.

Mouriquand (1926) observed a pellagra-like syndrome in guinea-pigs fed on maize or the ordinary ration with the omission of grass. The disorder was characterized by loss of hair, intestinal troubles and general dystrophy. The exact nature of the deficiency responsible for the condition was uncertain.

A somewhat similar pellagral disorder was produced by Scheunert and Lindner (1927) in albino rats on a diet containing too little vitamin B. These investigators were apparently unaware of the recent work by Goldberger and others in this field, and did not recognize the possibility of different factors in the vitamin B complex. It may be assumed, however, that their results (skin lesions) were probably due to a deficiency of the antipellagra (P-P) component. These lesions (which appeared in all their rats on the diet deficient in B over fifty days) began in the region of the eyes, with conjunctivitis, dermal hyperemia and depilation. Simultaneously, papillary outgrowths (not mite infection!) appeared around the nasal and oral apertures. On the limbs, especially the dorsum of the feet, there occurred similarly bilateral hyperemia, depilation, and epidermal desquamation with a copious exudate. Histologic sections sometimes showed also a slight cellular infiltration of the subcutaneous region. In general, the condition was considered as equivalent to pellagra in man.

The work of Chick and Roscoe (1927, 1928) directly confirmed the conclusions of Goldberger as to the effects of a deficiency of the antipellagra (P-P) factor. Their rats with pellagra usually maintained their weights and were active, though in poor condition. The urine often appeared slightly blood stained. The hair coat was rough and the hair dropped out in patches, leaving inflamed areas on the nose (sometimes on the ears) and on the backs of the forepaws. These areas were often edematous and tended to enlarge and spread around the nose and the mouth, the thorax, and the hind limbs. There was marked conjunctivitis. The rats continued two or three weeks in this condition before death occurred. The postmortem examination did not reveal any further abnormality, aside from an "unhealthy condition" of the whole alimentary tract. Especially the small intestine was inflamed and atrophic, containing bloodstained mucus.

Salmon (1927) likewise noted in rats on seed diets deficient in the growth-promoting factor of vitamin B "a tendency to lose their fur in patches and in a few cases to develop an inflammation of the eye." These were probably symptoms of the same pellagral disorder.

Findlay (1928) recently described the pellagra-like lesions in rats on diets deficient in vitamin F (B_2), confirming the results of Goldberger and his associates. He obtained the failure of growth with the characteristic lesions of the skin, oral mucosa, tongue and eyes, followed by death in two or three weeks. The liver, spleen, thymus and testes

were markedly subnormal in weight, the kidney nearly normal and the suprarenal glands above normal. Aside from those in the skin and the nervous system, the histologic changes in general resembled those of simple inanition. A papillomatous lesion found in the cardiac portion of the gastric mucosa was thought to be nonspecific for the deficiency of the vitamin.

The possible relation of pellagra to the "black-tongue" syndrome of dogs has received considerable attention. Underhill and Mendel (1925) concluded that the Chittenden-Underhill pellagra-like syndrome in dogs may be due to the lack of an unrecognized vitamin present in carrots and butter fat. Goldberger and his associates (1926, 1928) believed that their experimental pellagra in dogs was probably identical with the Chittenden-Underhill syndrome. The condition developed slowly, with a progressive stomatitis and variable lesions on the cheeks and tongue. Constipation was frequent, and was sometimes succeeded by final diarrhea (sometimes bloody). In from 40 to 50 per cent of the males, there was an area of pellagra-like eruption in the skin of the scrotal region; this area was reddened and sometimes pigmented, with desquamation. Lacrimation, convulsions and other symptoms were noted in a few cases. Occasional lesions of the alimentary or respiratory tract were observed at necropsy. Denton (1928) found the lesions in these animals similar to those of pellagra in man.

Denton (1925) made a thorough study of the pathologic changes of pellagra in man, based on sixteen cases in Panama. The essential clinical symptoms included the characteristic lesions of the skin, mouth and tongue, gastro-intestinal disturbances and symptoms referable to the central nervous system. "Pellagra is a disease in which the lesions are confined to epithelial surfaces without extension to deeper tissues or organs." The cutaneous lesions involved the following stages: injury, or the fibrolytic stage; reaction, or the dermatitic stage; repair; compensatory vascular ectasia, or the erythematous stage; the cicatricial, or atrophic stage. The brownish-red color of the oral and esophageal mucosae (with or without necrotic lesions), dark-red small intestine and variable degrees of colitis were gross characteristics. Most of the viscera did not show constant or important lesions. Variable degeneration (tigrolysis) of the nerve cells in the central nervous system was observed.

Sutton (1926) reported observations in fifty-six cases of pellagra, in five of which necropsies were recorded. The "unknown toxin" of pellagra attacked chiefly the ectodermal structures of the skin, the alimentary tract and the central nervous system, resulting in the familiar diagnostic tripod of dermatitis, diarrhea and dementia. The lesions of the skin and of the oral mucosa were described by Sutton in detail. At necropsy, there appeared atrophy and thinning of the alimentary canal,

with hyperemia and ulceration of the oral mucosa and lower bowel. Abnormal pigmentation was found in the ganglionic cells, heart muscle, liver and spleen. Atrophy of the lateral and (sometimes) posterior columns of the spinal cord was noted. Sutton did not accept Goldberger's theory that pellagra is caused by a deficiency of protein; he inclined toward the theory that it is caused by a toxin. Crutchfield (1928) studied especially the skin and mucosa in 109 cases with ten autopsies.

Klauder and Winkelman (1928) described the symptoms and other pathologic manifestations of pellagra in chronic alcoholic addicts, who seem especially predisposed to this disorder. The characteristic degeneration of the brain cells was observed by the Nissl method.

Other Vitamins (Vitamin G): Evans and Burr (1927a) observed that a highly purified diet of casein, sucrose and salts was not adequate for normal growth and ovulation in rats, even when this diet was supplemented by foods containing high levels of the vitamins A to E, inclusive. Since the deficiencies of growth and ovulation were corrected by the addition of small amounts of lettuce, liver or lard, it was concluded that these substances probably include a hitherto unrecognized factor of growth, for which the name vitamin F or H was suggested. In a further study (1928b), they found that the addition of lard to this diet of sugar and casein brought about better growth than did the addition of butter, coconut oil or corn oil; but that in supporting lactation the lard was the least effective of the three. Burr (1928) also discovered in rats on the diet of sugar and casein certain degenerative changes involving a necrosis of the tail. This disorder was prevented or cured by the addition of small doses of lard to the diet. If the term vitamin F is applied to the second B, or antipellagra, factor (as has been suggested) the new factor discovered by Evans and Burr seems the logical one for recognition as vitamin G.

McCay, Bing and Dilley (1928) described briefly the results of a feeding experiment on growing trout. A diet of purified rations (a mixture of casein, boiled starch and salt) proved inadequate, even when supplemented with all the known vitamins from A to E. The addition of raw liver resulted in excellent growth, however, and for the unknown factor in the liver they proposed the name "factor H." It seems quite possible that this factor may be identical with the new vitamin promoting growth discovered by Evans and Burr, for which the term vitamin G is now proposed.

It is not at all likely, however, that the list of vitamins is finally exhausted. Some or all of the vitamins now recognized are probably composite in character, and other undiscovered factors doubtless exist. Richardson, Palmer and Kennedy (1928) believed that the highly purified foods which they used, had been dispossessed of some unknown

substance that is essential for the utilization of fat by the body. It is indeed quite possible that before the knowledge of nutrition is complete all the letters of the alphabet will have been insufficient to designate the various vitamins and similar dietary factors involved.

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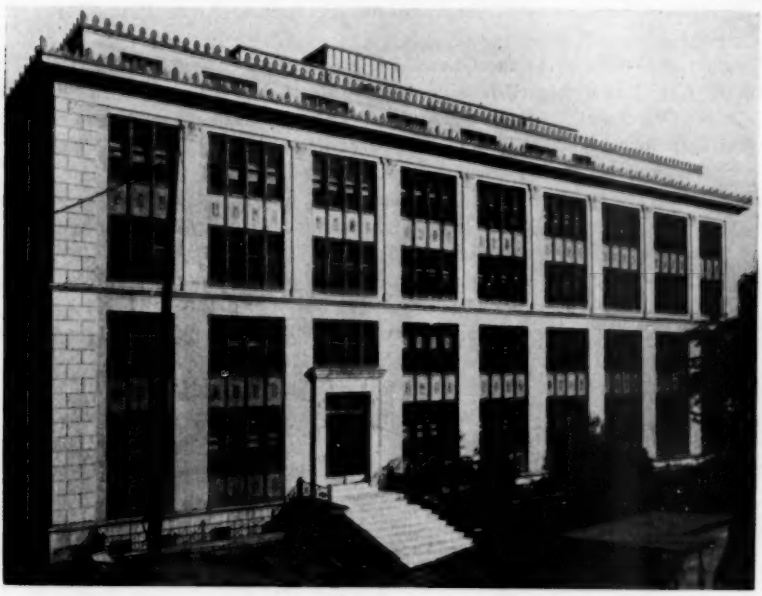
Notes and News

Dedication of Institute of Pathology, Western Reserve University.—In the autumn of 1926 the General Education Board appropriated $750,000 for the construction of an Institute of Pathology at Western Reserve University. After study of the situation it was decided that the building would house all the work in pathology of the university and the associated hospitals, including Lakeside Hospital, Babies' and Children's Hospital, Maternity Hospital and the Hanna Pavilion. It was further decided that the institute would serve as a central laboratory for the more intricate tests that deal with biochemistry, immunology and bacteriology. After careful consideration of similar buildings on this continent



Institute of Pathology, Western Reserve University.

and in Europe, plans were drawn by Abram Garfield of Cleveland. Ground was broken in February, 1928. The building was constructed by Crowell and Little of Cleveland, and was occupied in June, 1929.

The building is of buff brick and Indiana limestone. It consists of sub-basement, basement and five floors, the uppermost of which is for animal quarters. It is an oblong building, 160 by 60 feet, with steel framework, supported on forty steel columns. The sub-basement houses machine rooms and contains seven rooms for the storage of pathologic materials such as tissue blocks.

The basement contains a large museum which is designed so as to provide specimens for clinical teaching throughout the medical group. The morgue, chapel, undertakers' room, receiving room, living quarters for an orderly and stable for horses and sheep are found on this floor. An amphitheater runs through this floor and the first floor, projecting out over, and concealing, a ramp where delivery of bodies may be made under cover. The amphitheater contains 166 seats and has been given acoustic treatment.

The first floor is entirely for student purposes. The class room for pathologic histology has ample capacity for sixty-six students with an expansion capacity of ten more. A small auxilliary class room for demonstrations can accommodate fifty students. Communicating by dumb waiter with the museum preparation room below, is a room for the exhibition of gross morbid anatomic material. A room is provided for experimental work by the students. Student entrance to the amphitheater is from the first floor level. Locker rooms and toilets are provided for men and women students.

The second floor houses the departmental library, with a capacity of 10,000 volumes, stockrooms, a conference room, record rooms, nine rooms for staff with office and private laboratory facilities and a general experimental room for housing heavy apparatus. From this floor the staff can go down one flight to the class rooms or up one flight to the rooms for routine hospital work.

The third floor contains one office, a shop, a room for cleaning of glassware and preparation and sterilization of mediums, separate rooms for bacteriology, immunology and preparation of histologic material. Dental pathology has two large units on this floor. Biochemistry has four large units. There are three cubicles for investigators who come from outside the university group and these rooms share a common laboratory.

The fourth floor contains the general autopsy room with two tables, a private autopsy room with one table, and a preparation and store room between. The art suite combines a large room for the artist and a large room for gross and microscopic photography. A dark room serves the photographic room and an experimental x-ray room. There are eighteen rooms for members of clinical departments who wish to do research in subjects closely related to pathology. Sixteen of these are arranged in groups of four small rooms, with a common laboratory.

The fifth floor has a large space allotted to dogs, with built-in cages and a central open air court for exercise. Separate rooms are provided for rats and mice, birds and monkeys, rabbits and guinea-pigs, fish and frogs. There is a metabolism room for animals, a dark room for research with various types of light, an isolation room, a food storage and preparation room, a cage cleaning room, an inoculation room and a complete suite for surgical operations and physiologic experiments on animals.

Symbolic decorations have largely replaced conventional decorations throughout the building. Above the doorway are grouped low bas reliefs of the heads of representative pathologists from various countries: Morgagni, Italy; John Hunter, England; Bichat, France; Virchow, Germany; Rokitansky, Austria; Welch, America; Cohnheim, experimental pathology; and Pasteur, bacteriology and immunology. Bronze doors are decorated with zodiacal signs of Libra and Cancer, medieval lancets, medieval urine glass, pine cone and the Tudor rose. A frieze over the door alternates the cock and the pine cone. The panel over the door shows the American form of the caduceus over which is an open book with the inscription from Claude Bernard, "Observation shows and experiment teaches." Six designs are repeated in the panels under the windows and are the motifs from escutcheons of the medieval guilds; namely, Barber Surgeons of London, Physicians of London, Barber Surgeons of Brussels, Barber Surgeons of Edinburgh, and Apothecaries of Nuremberg with the shield of the Medici of the Della Robbia period representing Italy. Interior grilles utilize much the same material as the bronze doors. A frieze around the main corridor utilizes the caduceus and the pine cone. The lamp shades in the library are decorated with the trademarks of eight of the great medieval and early renaissance printers and publishers. The interior of the building is of simple construction with the exception of decorative features in the library, chapel, entrance hall and director's office.

The dedicatory exercises will take place Oct. 7, 1929, and a general invitation is extended to all who may be interested. The exercises will be presided over by the president of the university, Dr. Robert Ernest Vinson. Brief addresses will be made by President Vinson, Torald Sollmann, dean of the medical school, and

Howard T. Karsner, director of the institute. The dedicatory address will be delivered by Henry Roy Dean, professor of pathology in the University of Cambridge. Honorary degrees will be conferred on Professor Dean, Dr. William H. Welch, William T. Councilman, Ludvig Hektoen and Simon Flexner. Preceding the dedicatory exercises, which will take place at 5 o'clock in the afternoon, the building will be open for inspection. Following the dedicatory exercises a dinner will be given by President Vinson to the delegates from institutions of higher rank and the learned societies.

University News, Promotions, Resignations and Appointments.—Dr. Timothy Leary has resigned as professor of pathology, bacteriology and medical jurisprudence at Tufts College Medical School, Boston, after about thirty-two years of service.

Dr. George S. Silliman, Abingdon, has accepted a position as roentgenologist and pathologist at the Methodist Hospital, Gary, Ind.

Dr. Allan W. Blair, formerly of the Pathological Institute of the Royal Victoria Hospital, McGill University, Montreal, has been appointed instructor in pathology and bacteriology at the University of Alabama School of Medicine.

Dr. Jean R. Oliver, professor of pathology, Stanford University Medical School, San Francisco, has been appointed professor of pathology at the Long Island College Hospital, Brooklyn, to succeed Dr. Archibald Murray, the appointment to become effective July 1. Before going to Stanford, Dr. Oliver was with the Rockefeller Institute, New York.

The dean of the University of California Medical School, San Francisco, announces the following appointments and promotions in the faculty, effective July 1: Dr. Isabel H. Perry, pathology; Dr. Adelbert M. Moody, pathology; Dr. Stacy R. Mettier, assistant professor of medicine and pathology; Dr. Zera E. Bolin from instructor to assistant professor of pathology; Dr. James F. Rinehart from assistant to instructor in pathology.

Prof. Oskar Frankl of Vienna will give twenty lectures on gynecologic physiology and pathology, and ten lectures on endocrinology at the Woman's Medical College of Pennsylvania, September 10 to 26.

The following appointments for the next academic year have been made by the medical fellowship board of the National Research Council, of which Dr. Gotthelf Carl Huber, professor of anatomy, University of Michigan School of Medicine, is chairman: Claude Forkner, pathology and clinical investigation; Emidio L. Gaspari, bacteriology and immunology; Leone McGregor, pathology, and Bruce Webster, internal medicine.

Milwaukee Academy of Medicine.—The Milwaukee Academy of Medicine was addressed on May 28, by Dr. Charles H. Bunting, professor of pathology, University of Wisconsin Medical School, on "Diseases of the Bone Marrow and Lymph Glands."

American Psychopathological Association.—Dr. James Ramsay Hunt, New York, was elected vice president, and L. E. Emerson, Cambridge, Mass., secretary, of the American Psychopathological Association at a meeting held in Atlanta, Ga., on May 17.

Cancer Registry Established.—Local physicians will establish city-wide cancer and abnormal growth registry, at the Research Institute of the Lankenau Hospital in September. All types of tumors will be preserved to assist the diagnosis and study of these growths. A feature of the registry will be a follow-up service in which nurses provided by the Philadelphia Health Council will visit patients after they have had cancerous or noncancerous growths removed to report to what extent surgical treatment has been beneficial. The registry is being organized by Dr. Stanley P. Reimann, director of the research institute of the hospital. Its head will be Dr. Joseph McFarland, professor of pathology, University of Pennsylvania School of Medicine.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

JUVENILE ACRODYNIA. C. W. WYCKOFF, Am. J. Dis. Child. **37**:88, 1929.

The author, by a process of elimination, arrives at the conclusion that a subacute infection is the cause of acrodynia. The symptoms are objective. Extreme restlessness, sleeplessness and irritability are manifest. The child never plays, and it lies down in a crouching position with the abdomen supported by the thighs. The cardinal symptom is redness and swelling of the extremities with desquamation. The remaining symptoms are anorexia and asthenia. The child becomes emaciated, a rash appears, teeth fall out and there is a diminution of sensitiveness to external stimuli. Byfield claims that the condition is one of peripheral neuritis involving mainly the sensory nerves and showing marked vasomotor disturbances of the extremities. The treatment advised consists of removal of the tonsils and adenoids. The use of hypnotics is not advisable. Calamine lotion is used for the eruption of the skin and itching. The main object in treatment is to maintain a fair state of nutrition.

H. E. LANDT.

HYPERTENSION IN THE YOUNG. SAMUEL AMBERG, Am. J. Dis. Child. **37**:335, 1929.

Different forms of hypertension, persisting for long periods, can occur in childhood. The cases reported here represent: (1) hypertension associated with coarctation of the aorta—in these cases the elevation in blood pressure is confined to the upper part of the body; (2) hypertension associated with cardiac decompensation; (3) hypertension intimately associated with disease of the kidney—in such cases it may be of shorter or longer duration and at times be referable to increased intracranial pressure; (4) hypertension as the consequence of an organic cerebral lesion; (5) hypertension perhaps in the form of so-called essential hypertension, and (6) hypertension in the form of a syndrome of malignant hypertension as described by Keith, Wagener and Kernohan, with changes mainly in the small arteries and arterioles.

AUTHOR'S SUMMARY.

MUSCULAR HYPOTONIA ASSOCIATED WITH CONGENITAL HEART DISEASE. C. DAVISON and MORRIS M. WEISS, Am. J. Dis. Child. **37**:359, 1929.

A case of congenital heart disease associated with a marked hypotonia is reported. If the hypotonia is an anomaly, as others occurring in a congenital cardiac condition, then this is the first case of its kind reported. If the hypotonia does not have a relationship to the cardiac condition, the only disease that it simulates is amyotonia congenita, in which case it would be an atypical form of this entity.

AUTHORS' SUMMARY.

THE PROGRESSIVE ANEMIA FOLLOWING A SINGLE INTRAMARROW INJECTION OF B. WELCHII TOXINS. JOHN C. TORREY and MORTON C. KAHN, Am. J. Path. **5**:117, 1929.

It has been found that the single inoculation of 0.5 cc. of a potent sterile *B. welchii* toxin into a tibial marrow of a rabbit or a monkey gives rise to a chronic, persistent and finally often fatal anemia, characterized by low hemoglobin content of the blood, low erythrocyte count and a color index generally above 1. Anisocytosis and at times poikilocytosis are pronounced. A single intravenous inoculation of *B. welchii* toxin of the same dosage, or a series of increasing doses, gives rise to an anemia of the same type as that resulting from inoculation of the marrow, but is followed within from three to four weeks by an immunity and a

return of the blood to a normal or nearly normal condition. Such intravenous inoculation of the toxin causes some mucous degeneration of the fat cells and an increase in the cellular elements in the marrow, particularly the leukocytes, but results in nothing like the destructive action of inoculation directly into the marrow. The single inoculation of 0.5 cc. of the toxin into a tibial marrow starts a degenerative process which apparently affects the whole marrow system. Definite evidence of beginning degenerative changes were noted in the marrows on the side of the body opposite the site of inoculation within eighteen hours. After twelve days the process was well advanced as shown by the marked mucous degeneration of the fat cells, great diminution in other normal marrow and blood-forming cells and a marked increase in polymorphonuclear leukocytes. In rabbits which had died eleven or more weeks after the inoculation the marrows were found to be in an advanced stage of degeneration, with fat cells replaced by a granular material and an extreme atrophy of the cellular elements. Nearly all the animals showed, at whatever stage examined, a rather more pronounced degeneration in marrows far removed than in that into which the toxin was injected. As intravenous inoculation of like or larger amounts of toxin causes no more than a transitory injury to the marrow, the cause of the difference in effect is not clear. It is suggested that the chronic experimental anemia produced in this way may prove a useful means for evaluating the potency of extracts of liver and other organs as blood regenerating agents.

AUTHORS' SUMMARY.

THE SYNDROME PRODUCED BY ANEURYSM AT OR NEAR THE JUNCTION OF THE INTERNAL CAROTID ARTERY AND THE CIRCLE OF WILLIS. FULLER ALBRIGHT, Bull. Johns Hopkins Hosp. **44**:215, 1929.

The symptoms in two patients, on whom the diagnosis of ruptured intracranial aneurysm near the junction of the internal carotid artery and the circle of Willis was made, are reported with the results of autopsy in one case. Thirty cases of aneurysm in this region in which there were localizing symptoms before death are abstracted from the literature. The entire series of thirty-two cases fall into five etiologic groups: mycotic, traumatic, syphilitic, arteriosclerotic and congenital. The symptomatology can be divided into two main subgroups, neighborhood symptoms due to involvement of structures in this region, and symptoms arising from leakage of blood into the subarachnoid space. The neighborhood symptoms, except in the larger aneurysms, as a rule become manifest only after partial rupture of the aneurysm and the formation of a false aneurysm. The commonest neighborhood symptoms are internal and external paralysis of the third nerve and involvement of the first branch of the fifth nerve. The third nerve was involved in every case in the series. Relief of pain by obliteration of the common carotid artery in the neck was a helpful diagnostic sign in one of my cases. The internal carotid artery was ligated in the neck without success in one of the newly reported cases. The possibility of relieving this condition by surgical measures is discussed, but no conclusions are reached.

AUTHOR'S SUMMARY.

OUTLYING ACIDOSIS DUE TO FUNCTIONAL ISCHEMIA. PEYTON ROUS and DOUGLAS R. DRURY, J. Exper. Med. **49**:435, 1929.

In various functional conditions involving peripheral vasoconstriction, a more or less widespread change toward acidity takes place within certain tissues. The change is frequently independent of any in the blood. Indeed, the blood can become more alkaline while the tissue acidosis is developing. When the blood volume is diminished abruptly but not too greatly, by hemorrhage or by anhydremia, the acidosis which develops in the superficial connective tissue and in the skeletal muscles is patchy in distribution, being limited to areas of local ischemia themselves the result of a compensatory vasoconstriction which affects certain regions only. There is a second type of patchy ischemia (and of acidosis) which occurs under circumstances of moderate depletion and is referable to local pressure differences

that are so slight as to be ineffective under normal circumstances. A generalized acidosis throughout the superficial tissue develops when depletion is extreme. All these are outlying acidoses, since they lie without the influence of the blood. In the viscera no such acidoses have been found.

AUTHORS' SUMMARY.

TREATMENT OF EXPERIMENTAL ACUTE GENERAL PERITONITIS IN THE DOG WITH ILEOSTOMY AND SODIUM CHLORIDE SOLUTION. THOMAS G. ORR and RUSSELL L. HADEN, J. Exper. Med. **49**:525, 1929.

In experimentally produced general peritonitis, drainage of the gut by ileostomy 6 inches (15.24 cm.) above the cecum has no beneficial effect. Animals with experimentally produced general peritonitis treated with ileostomy plus 1 per cent sodium chloride solution live three times as long as those not given the salt solution.

AUTHORS' SUMMARY.

THE RAPID SHALLOW BREATHING FROM PULMONARY CONGESTION AND EDEMA. EDWARD D. CHURCHILL and OLIVER COPE, J. Exper. Med. **49**:531, 1929.

These experiments record the effects of the experimental production of pulmonary congestion and edema in a lung completely isolated from the general circulation, but with an intact nerve supply. The resulting changes are: a slowing of the heart rate, a fall in systemic blood pressure and a temporary inhibition of respiration succeeded by rapid shallow breathing. The pulse rate and blood pressure show a rapid and spontaneous return to initial conditions. The respirations show a partial but not a complete return to their former rate and depth. The effects on respiration are similar to those described by Dunn and Binger and Moore which follow multiple embolism of the pulmonary circuit with starch granules. The alterations in the pulse rate and blood pressure are characteristic of the effects of vagal stimulation. A chemical effect on the respiratory center is excluded by the nature of the preparation. These results, therefore, add further evidence to support the hypothesis that the rapid shallow breathing present in congestion and edema of the lungs is due to the stimulation of nerve endings in the lungs.

AUTHORS' SUMMARY.

BLOOD CHLORIDES IN CONDITIONS ASSOCIATED WITH PNEUMONIA. CARL A. L. BINGER, RONALD V. CHRISTIE, JOHN STAIGE DAVIS, JR., and ALMA HILLER, J. Exper. Med. **49**:603, 1929.

Attempts have been made in dogs to lower the chlorides in the serum by means of various procedures. Of these the withholding of food, anoxemia, tissue destruction, anaphylactic shock, leukocytosis and fever yielded negative results. The ingestion of large amounts of water lowered the chloride level independently of body temperature. The drop in chlorides under these circumstances could not be accounted for by excretion and appeared to run parallel with an increase in the water content of the serum. Experimental pneumococcus infection in two animals reduced the chloride concentration in the serum.

AUTHORS' SUMMARY.

ARTERIAL CARBON DIOXIDE PRESSURE IN CARDIAC DYSPNEA. F. R. FRASER, C. F. HARRIS, R. H. HILTON and G. C. LINDER, Quart. J. Med. **22**:1, 1928.

Fifty cubic centimeters of blood was drawn from the femoral arteries of patients with cardiac dyspnea into paraffined syringes containing potassium oxalate and sodium fluoride. This was kept surrounded by ice. Four portions of 10 cc. each were successively transferred to tonometers of 400 cc. capacity, filled with mixtures of air and carbon dioxide so that the pressure of carbon dioxide was 20, 30, 40 and 50 mm. of mercury. The volume of carbon dioxide in the blood from the tonometer was plotted against the pressure of carbon dioxide in the tonometer, and a dissociation curve constructed. The point in the curve corresponding to the volume of

carbon dioxide in the arterial blood gave an estimation of the arterial carbon dioxide pressure. This was further checked by plotting the carbon dioxide pressure in the tonometer against the hydrogen ion concentration of the blood removed from the tonometer. The results of this study indicate that in the absence of such factors as pulmonary disease and the changes that occur in dying tissues cardiac dyspnea is characterized by a low carbon dioxide pressure in the arterial blood. As the degree of heart failure and the dyspnea diminish, the pressure of the carbon dioxide rises. The low carbon dioxide pressure is associated with an arterial hydrogen ion concentration which is on the alkaline half of the normal range. This is significant in that it indicates that an increased acidity of the blood supplied to the respiratory center is not the cause of the increased respiratory activity. The combination of the low carbon dioxide pressure and the low normal carbon dioxide capacity, and the values of the hydrogen ion on the alkaline side are indicative of a dyspnea due to the stimulation of the respiratory center, but which is independent of the character of the blood supplied to the center. Thus, this stimulus may be due to low oxygen tension in the tissues of the center, which would result from a lowered minute volume of the circulation. In those cases in which there is pulmonary disease in addition to heart failure, or those in which pulmonary lesions are seen in severe passive congestion, the arterial carbon dioxide pressure is raised. This is probably the result of inefficient pulmonary ventilation, and the raised carbon dioxide acts as an additional stimulus to the respiratory center. An additional factor is the increased hydrogen ion concentration which occurs shortly before death; this would act as an additional stimulus to the center.

N. ENZER.

GOUT. P. E. A. NYLANDER, Arb. a. d. Path. Inst. d. Universität. Helsingfors **5**: 381, 1928.

It is probable that gout is related to vasomotor and trophic neuroses. That disturbances of calcium metabolism play a rôle in gout is not established; the calcareous deposits in gout are probably not the direct result of increase in the blood calcium.

THE GASEOUS METABOLISM IN TUBERCULOSIS WITH SPECIAL REFERENCE TO THE SPECIFIC-DYNAMIC ACTION OF PROTEINS. F. SALUS and H. ADLER, Beitr. z. Klin. d. Tuberk. **70**:733, 1928.

The basal metabolism in afebrile, noncachectic tuberculous patients may be normal, increased or decreased. Basal metabolic determinations cannot be used for the diagnosis of activity. Tuberculous patients show frequently greater fluctuations in the basal metabolic rate than normal persons. Artificial pneumothorax has no influence on the basal metabolic rate. The specific-dynamic action of proteins was found decreased in 15 per cent, normal in from 15 to 30 per cent and increased in more than 30 per cent of the patients. These deviations do not show any correlation with the pulmonary process, but they are definitely dependent on the allergy of the patient. Increased protein action is frequently associated with alimentary hyperthermia. These studies suggest that a diet low in proteins may be indicated in certain tuberculous patients.

MAX PINNER.

CHANGES ACCOMPANYING WORK AND FATIGUE OF MUSCLE. L. WACKER, Klin. Wchnschr. **8**:244, 1929.

The content of calcium and magnesium is increased considerably in the blood of rabbits fatigued by an alternating electrical current during urethane narcosis. The increase of the calcium in the serum averages 50 per cent, and of the magnesium about 140 per cent, that of the resting values in urethane narcosis. The increase in magnesium is relatively greater than that in calcium. The quotient $\frac{Ca.}{Mg.}$ diminished from $\frac{10.84}{2.93} = 4.16$ in the nonfatigued animal to $\frac{18.03}{7.01} = 2.57$ in the fatigued animal. The increase of calcium and magnesium in the blood with

fatigue disappears after several hours of rest. The high calcium and magnesium content of the blood in fatigued animals is derived probably from the muscle, the bases being liberated from the earthy phosphates dissolved by the muscle acidity and then transferred to the blood. With magnesium narcosis the magnesium content of the serum exceeds the calcium and the $\frac{Ca.}{Mg.}$ quotient $\frac{9.40}{19.41}$ diminishes to 0.48. Part of the calcium is replaced by magnesium. In the normal rabbit serum the calcium is 11.84 mg. per hundred cubic centimeters; in the narcosed animal 9.40 mg. per hundred cubic centimeters.

AUTHOR'S SUMMARY.

OVARIAN HORMONE AND METABOLISM. GERTRUD KOEHLER, Klin. Wchnschr. **8**:502, 1929.

The metabolic rate in eight women and two men was not altered by the administration of ovarian hormone.

EDWIN F. HIRSCH.

CARBOHYDRATE METABOLISM AND THE OXIDATION OF THE GLUCOSE MOLECULE. E. SCHNEIDER and E. WIDMANN, Klin. Wchnschr. **8**:536, 1929.

Lactic acid injected intravenously is synthesized to glycogen. Dioxyaceton is completely oxidized. Methylglyoxal, on the contrary, to some extent is synthesized to glycogen through lactic acid.

AUTHORS' SUMMARY.

Pathologic Anatomy

HEART-BLOCK SHOWING MULTIPLE TRANSITIONS ASSOCIATED WITH CONVULSIVE SYNCOPE. WALLACE M. YATER and FREDERICK A. WILLIUS, Am. Heart J. **4**:280, 1929.

A case is reported with detailed pathologic data. Also, the literature on the pathology of heart block is reviewed briefly and a bibliography is furnished. Directions are given for taking sections at the autopsy table to aid in locating the lesions in heart block.

PEARL ZEEK.

HEMANGIOBLASTOMA OF THE CEREBELLUM (LINDAU'S DISEASE). LEO M. DAVIDOFF, Am. J. Path. **5**:141, 1929.

The practical importance of a knowledge of these tumors is, in the first place, that when they occur alone they are completely removable surgically with a resulting cure of the condition. Secondly, in the presence of all tumors of the cerebellar hemispheres, one must, knowing the associated lesions in cases of Lindau's disease, be on the lookout for angiomatosis retinae and tumors of the medulla, spinal cord, pancreas, kidneys, suprarenal glands, epididymi, etc., especially if material gained by operation proves histologically to be hemangiomatous in character. The prognosis in the complicated cases should be guarded even if the cerebellar tumor is removed in its entirety.

AUTHOR'S SUMMARY.

THE EFFECT OF COMBINED FEEDING OF POTASSIUM IODIDE AND ANTERIOR LOBE OF THE PITUITARY UPON THE THYROID GLAND. HOWARD ANDERSON MCCORDOCK, Am. J. Path. **5**:171, 1929.

Oral administration of anterior pituitary tablets causes a depression in the activity of the thyroid gland with a marked lowering of the number of mitoses in the entire gland and with medium-sized or somewhat smaller acini distended with hard colloid compressing the lining epithelium into thin strands of cells. During the first stage of its action, potassium iodide, on the other hand, produces marked stimulation with enormous mitotic activity and a slightly softened colloid occasionally containing large numbers of phagocytic cells. The early proliferative change induced in the thyroid gland by potassium iodide is prevented by anterior pituitary when both these substances are fed to the same animal.

AUTHOR'S SUMMARY.

FENESTRATIONS OF THE SEMILUNAR VALVES. ARTHUR N. FOXE, Am. J. Path. **5**:179, 1929.

In a series of 300 cases, one or more fenestrations occurred with a frequency of 82 per cent. The frequency of pulmonic and aortic involvement was approximately equal. Fenestrations, which are acquired defects, increase in frequency with age. Patent foramen ovale, which is a developmental defect, decreases in frequency with age. The total percentage for the frequency of the occurrence of this defect was 22. The classification, nature and variety of the fenestrations are briefly discussed. It is possible that fenestrations may occasionally cause an aortic insufficiency.

AUTHOR'S SUMMARY.

INTRA-MEDULLARY LIPOMA OF THE SPINAL CORD. E. SACHS and E. F. FINCHER, Arch. Surg. **17**:829, 1928.

A lipoma beneath the dura, at the level of the sixth thoracic vertebra, was found to be imbedded in the cord. Sections showed it to be composed entirely of fatty tissue. The condition is rare. One writer previously collected nine cases, some of which the authors feel are not pure lipomas. Of fourteen intramedullary tumors reported by Elsberg, not one was lipomatous.

N. ENZER.

HEMANGIOMA OF THE KIDNEY. H. H. CRILE, Surg. Gynec Obst. **48**:449, 1929.

A 6 by 6 cm. cystic and fluctuating cavernous hemangioma, located on the anterior aspect of the anteroexternal surface of the kidney, produced sudden severe pain in the right lower abdominal quadrant and the passage of blood clots in the urine in a white man, aged 37. No communication was found between the tumor and the pelvis of the kidney although the remaining portion of the renal calices contained blood. The microscopic picture was that of a typical cavernous hemangioma.

RICHARD A. LIFVENDAHL.

ABERRANT BLOOD VESSELS AS A FACTOR IN LOWER URETERAL OBSTRUCTION. JOSEPH A. HYAMS, Surg. Gynec. Obst. **48**:474, 1929.

An aberrant artery running in a band of fibrous tissue caused constriction of the right ureter, from 6 to 8 cm. above the ureteral orifice. Proximal to this constriction there was a calculus, above which the ureter was dilated. The patient suffered sharp intermittent pains over the sacro-iliac region and the kidneys at intervals of five or six months for a period of three years. From dissection of cadavers the author found that there was considerable variation in the course and distribution of the vessels of the pelvis in the vicinity of the ureters. In one body he noted a similar constricting band of the ureter as in the aforementioned patient.

RICHARD A. LIFVENDAHL.

CONGENITAL VALVULAR OBSTRUCTION OF THE PROSTATIC URETHRA. H. H. YOUNG and R. W. MCKAY, Surg. Gynec. Obst. **48**:509, 1929.

The authors report fifty-one cases of congenital valvular obstruction of the urethra in persons from 11 days to 57 years of age. The condition is described as an obstructing fold of mucous membrane coming from the vesicle neck in the form of semilunar valves, as a diaphragmatic membrane below the verumontanum, or as a fold running downward from the prostatic orifice anteriorly. As a result of this obstruction to the outflow of urine there is a funnel-shaped dilatation of the prostatic urethra and vesicle neck. If the obstruction is marked or if the condition is of long duration, the urinary bladder, ureteral orifices, ureters and the renal pelves may be markedly dilated. The authors divide the condition into three types depending on the position and character of the obstructing valves. The importance of early cystoscopic examination, the prognosis and the treatment are discussed.

RICHARD A. LIFVENDAHL.

THE BLOOD SUPPLY OF THE THYROID GLAND WITH SPECIAL REFERENCE TO THE VASCULAR SYSTEM OF THE CRETIN GOITRE. O. H. WANGENSTEIN, Surg. Gynec. Obst. **48**:613, 1929.

The blood supply of thirty-nine thyroid glands was studied after intra-arterial injection, with the glands submerged in normal physiologic solution of sodium chloride, some following the instillation of diluted ink, in a few cases, roentgen examinations followed the injection of mercuric oxide and Hill's white paste. The inferior thyroid artery was found to be considerably larger than the superior, and in several of the cretin goiters the former had a diameter of 9 mm. In the seventeen specimens from necropsy the inferior thyroid was absent but the superior was always found; in two the vessel was small. One gland had a double superior thyroid artery. An accessory thyroid artery was observed twice in dissected postmortem specimens. An anomalous artery, in one cretin patient, which arose as a branch from the main division of the right superior thyroid artery ran obliquely across the isthmus and communicated with the left inferior thyroid artery. The free anastomosis between the subcapsular vessels was well demonstrated in the various methods of injection. There seemed to be no direct relation between the size of the goiter and its arteries. A few injections of the veins revealed great friability of their walls with rupture and dissemination of the injected material into the adjacent tissue.

In cretin goiters intimal thickening was frequently observed, and in many instances almost complete occlusion of the lumen was noted in the arteries of the capsule and in those of the second order; even the follicular and interlobar branches were the site of degenerative changes. The muscular walls of the larger groups of vessels were often very thin. The interfollicular network of colloid goiters was narrowed and compressed, and their capillary communications were often absent. The adenomatous glands revealed changes similar to those of the cretin goiters; in both, areas of hyperplasia were surrounded by capillaries which appeared more like the normal vessels. This marked enlargement of the extra-glandular vessels is regarded as a compensatory effort to bring as good blood supply as possible to the adenomatous areas of physiologically hypo-active tissue, as alterations in the stroma have made a normal nutrition impossible.

RICHARD A. LIFVENDAHL.

ADENOMA OF THE KIDNEY. H. L. KRETSCHMER and C. DOEHRING, Surg. Gynec. Obst. **48**:629, 1929.

A thick bluish-white membrane, from 0.5 to 1 mm., encapsulated a tumor, 12 by 15 by 15.5 cm., weighing 760 Gm. that arose from the right kidney, leaving a small residual portion of the kidney which was located on the upper pole of the tumor. This mass, which was of uniform consistency, was composed of cuboidal or hexagonal cells in more or less alveolar arrangement. The nuclei of the cells were large and contained an abundant chromatin content. In the literature sixteen similar cases were found, the youngest in a girl, 11 months of age. The genesis is ascribed to rests of renal tubules, error in development, remnants of the Wolffian body, or the possibility the tumor cells may be the offspring of cells which were destined to form kidney substance but were early diverted to the formation of a tumor. There has been no recurrence four years after the removal the adenoma in the case described.

RICHARD A. LIFVENDAHL.

TORTICOLLIS; REMOVAL IN EARLY LIFE OF THE FIBROUS MASS FROM THE STERNOMASTOID MUSCLE. H. LEROY VON LACKUM, Surg. Gynec. Obst. **48**: 691, 1929.

Four infants with congenital torticollis with localized swellings in the sternomastoid muscles obtained marked relief after the removal of thick scar tissue from the muscle. Microscopically, this tissue consisted of connective and dense scar tissue in which muscle fibers occurred singly and in groups.

RICHARD A. LIFVENDAHL.

SQUAMOUS CELL CARCINOMA IN A DERMOID CYST OF THE OVARY. J. C. MASSON and N. C. OCHSENHIRT, Surg. Gynec. & Obst. **48**:702, 1929.

Three cases of squamous cell carcinoma in dermoid cysts are added to thirty-three which were previously reported. The importance of careful microscopic examination of every dermoid cyst of the ovary is emphasized.

RICHARD A. LIFVENDAHL.

CONGENITAL ECTODERMAL DEFECT. H. MACKAY and A. M. DAVIDSON, Brit. J. Dermat. **41**:1, 1929.

Eleven instances of hypotrichosis, dental aplasia, and disturbance in taste and smell are reported in five generations of the same family. The facial expression is characteristic and the glands of the skin are absent or rudimentary.

A RARE VOLUMINOUS LEIOMYOMA OF THE LUNGS. ENRICO EMILIO FRANCO, Tumori **3**:27, 1929.

At the autopsy of a woman, aged 56 years, Franco found in the upper lobe of the right lung an ovoid tumor mass measuring 13 by 11 cm.; attached to its side there was a second mass, about one-half the size of a hen's egg. On microscopic examination the tumor proved to be a fibro-myoma. No primary growth was discovered elsewhere in the body.

W. OPHÜLS.

MORPHOLOGY AND PHYSIOLOGY OF THE NORTH AMERICAN GOITER. C. ALEXANDER HELLWIG, Arch. f. klin. Chir. **154**:1, 1929.

Of 160 goiters obtained by operation at the Halstead Hospital, Halstead, Kan., 53 per cent were diffuse and 47 per cent nodular. Congenital goiters were not observed. The diffuse hyperplasias in puberty and pregnancy were macrofollicular colloid goiters. Microscopic examination revealed the surprising fact that two thirds of the so-called primary exophthalmic goiters were developed from the diffuse colloid goiters. Only 4 per cent of the thyrotoxic patients had parenchymatous (fetal) adenomas. Seventy-five per cent of the nodular goiters were composed of small multiple colloid nodules. The majority of those goiters caused thyrotoxic symptoms, usually not before the age of 40 years.

AUTHOR'S SUMMARY.

PLEURAL EFFUSIONS: THEIR MORPHOLOGY. A. ARNSTEIN and M. HUPPERT, Beitr. z. Klin. d. Tuberk. **70**:660, 1928.

The cytologic observations in 115 pleural effusions are reported. It is pointed out that effusions of various etiology (hydrothorax, tumors and inflammatory exudates) cannot safely be differentiated by morphologic examinations. Certain characteristics, such as hemorrhagic appearance and lymphocytosis, may be helpful in arriving at a diagnosis.

MAX PINNER.

HISTOLOGIC EXAMINATION OF CAVITIES AND BRONCHIECTASIS: THE HEALING OF CAVITIES. E. MELZER, Beitr. z. Klinik. d. Tuberk. **70**:694, 1928.

Complete anatomic healing of a cavity was not found in any of the examined patients. The histologic differentiation between healed cavities and bronchiectasis is possible in most of the cases. Bronchiectasis must be diagnosed if any one of the following structures are found in the wall: high cylindrical epithelium, circular or longitudinal smooth musculature, circular elastic fibers, or cartilage. When cavities shrink, bronchiectasis with small inflammatory changes may develop in the neighborhood; these are caused by the mechanical tension of the tissue.

MAX PINNER.

ENDEMIC GOITER IN THE HOG. EDUARD CLERC, Zieglers Beitr. z. path. Anat. u. z. allg. Path. Kinderh. **76**:444, 1928.

Thyroid glands of the hog, obtained in the goiter belt of Bern (Switzerland) were compared with those from the northern coast of Germany. As early as in the first year of life the Swiss hogs show a distinct diffuse enlargement of the thyroid gland. Its histologic structure coincides entirely with that of human goiter and that of other animals. The first change in goiter formation is epithelial hyperplasia which either persists or, after some time, is converted into colloid goiter. The iodine content of the glands of Swiss hogs was much less than that in the German hogs. The incidence of goiter does not differ only in the same village, but also in animals of the same pen. Lack of iodine, therefore, cannot be regarded as the only factor in producing goiter; neither can the quantity and quality of the food and water play an important rôle. The hyperplastic goiter in pigs is accompanied, as a rule, by a low body weight.

C. A. HELLWIG.

VITAL STAINING REACTIONS OF THE LUNG. G. SEEMANN, Beitr. z. path. Anat. u. z. allg. Path. **79**:1, 1927.

In continuation of previous work. Seemann studied the reaction of the lung to finely dispersed colloid (trypan blue), coarsely dispersed colloid (saccharated ferric oxide), and fine and coarse particulate matter in suspension (red mercuric sulphide and staphylococci). In most of the experiments, the mouse was used, and in a few, rats and rabbits. The material was introduced chiefly intravenously; in some experiments the intrapleural and intratracheal routes were employed. Wide difference of opinion still exists as to the relative activity of the capillary endothelium, the histiocytic elements and the alveolar epithelium of the lung in the matter of vital storage. Seemann found the lung taking up much less of the injected material than the liver or spleen. The capillary endothelium stored none of the injected materials. The alveolar epithelium was also inactive after intravenous injection, except in the cases of trypan blue. This caused a finely granular stippling of the nucleated alveolar lining cells, in contrast to the histiocytes in which the material was coarsely granular. Except for the small amount of trypan blue held by the alveolar epithelia, all of the stored material was in histiocytes and leukocytes. It was impossible to remove all the cells from within the vessels of the lung by perfusion, but the author believes that the storing histiocytes which he observed came from the blood stream and that the lung contains few or no elements belonging to the reticulo-endothelial system. Introduced intratracheally, cellular elements which the author holds to be alveolar epithelial actively phagocytized particulate matter; he concluded that the dust cells of the lung are epithelial in origin. Seemann reports the results of the parenteral introduction of foreign protein (casein and egg white) in solution. A single injection caused no demonstrable changes in the lung, contrary to the previously reported observations of Eller and of Siegmund, who had described vascular proliferative changes which often made their appearance from thirty to sixty minutes after the injection. Repeated injections also caused no changes in the lungs, but led to active hemopoiesis in the lymphoid tissues and in the spleen pulp. Protracted anaphylactic shock did not cause the swelling of the pulmonary capillary endothelium which was described previously by Domagk.

O. T. SCHULTZ.

AMNIOTIC ADHESIONS. J. OLOW, Beitr. z. path. Anat. u. z. allg. Path. **79**:27, 1927.

On the basis of two cases studied in detail, Olow concludes that amniotic adhesions result from incomplete dehiscence of the ectodermal epithelium of the embryoblast in the formation of the amniotic cavity. A multilocular instead of a unilocular cavity is thus formed. During further development the septums are transformed into strandlike and membranous adhesions.

O. T. SCHULTZ.

DISTRIBUTION OF LIPOIDS AND GLYCOGEN IN NORMAL TISSUES. H. ARNDT, Beitr. z. path. Anat. u. z. allg. Path. **79**:69, 1927.

Arndt sought to gain insight into the cellular metabolism of fat and carbohydrate by microchemical study of the morphologic distribution of these substances in the tissues of a number of species of domestic animals. Of methods for demonstrating carbohydrates, only those for glycogen were found useful. The hope of detecting an interrelationship between lipoid and carbohydrate materials within the cell was defeated by the fact that the methods for detecting the two groups of substances could not be applied to the same section. Both lipoid substances and glycogen could often be seen in the same cell, but there was no way of determining an intracellular transformation of one into the other. The relative distribution of fat and glycogen in the lobule of the liver, the former being in the central zone and the glycogen being at the periphery, may permit the theoretical deduction that fat is transformed into glycogen where intracellular metabolism is more active. Glycogen was never found within the nuclei of the freshly fixed tissues of lower animals; this suggests that its fairly frequent intranuclear occurrence in human tissues is the result of a pathologic process.

O. T. SCHULTZ.

ISLANDS OF CARTILAGE IN VERTEBRAL BODIES. W. PUTSCHAR, Beitr. z. path. Anat. u. z. allg. Path. **79**:150, 1927.

In a woman who died of mammary carcinoma with metastases in the cervical vertebrae, islands of cartilage were found in the bodies of the affected vertebrae. To determine whether the presence of the cartilage bore any relation to the carcinoma or was only a chance association, the vertebrae were examined in seventy-two bodies of persons ranging in age from 10 days to 85 years. As a rule, the examination was limited to the two lower thoracic and the two first lumbar vertebrae. Cartilage was found in fifty-four cases, the youngest being 15 years old. In ten children under 15 years of age, no cartilage was found, indicating that the presence of cartilage in the vertebral bodies was not the result of embryonic maldevelopment. When present it occurred in the form of islands, usually about a millimeter in diameter, embedded within the bone. The islands were often multiple, sometimes coalesced with each other, and occasionally reached a diameter of from 5 to 10 mm. Sometimes the cartilage occurred as downgrowths directly continuous with the cartilaginous plate covering the vertebral body. The author believes that the misplaced cartilage results from resorption of bone about blood vessels which enter the bone, and subsequent mechanical displacement of cartilage from the surface plate into the defect thus produced. The misplaced cells then grow into the marrow spaces of the bone. When present in sufficient amount the cartilage may cause structural weakness of the bone.

O. T. SCHULTZ.

PATHOLOGY OF SUPRARENAL GLANDS IN RELATION TO ADDISON'S DISEASE. W. KOVÁCS, Beitr. z. path. Anat. u. z. allg. Path. **79**:213, 1928.

In the frequent tuberculous involvement of the suprarenal glands in Addison's disease, the destruction is usually so great that it is impossible to reach a conclusion as to the relative importance of medulla and of cortex in the syndrome. As a contribution to the solution of this problem and to the pathology of the suprarenal glands, Kovács presents a careful study of several interesting cases, together with the deductions which he thinks may be drawn from them. In a woman, aged 48 years, who had had the typical pigmentation of Addison's disease for many years but whose blood pressure was normal, the suprarenal glands were greatly reduced in size and consisted only of medulla. The cortex was almost entirely absent; it consisted only of the degenerated remnants of a few regenerated islands. Kovács ascribes the disappearance of the cortex to a toxic material which acted specifically on the cortical cells. He excludes a toxic infectious process by the absence of scar formation, and postulates the action of a toxic material derived from abnormal metabolism. The resulting cytotoxic atrophy of the cortex he

likens to the contracted kidney observed in gout. Because of the similarity he prefers the name contracted suprarenal gland to atrophy. The toxic destruction of cortical cells continued over a long period of time and was associated with localized, nodular regeneration of cortical tissue, which served to maintain life until the final degeneration of the regenerated islands. This case is one of Addison's disease with suprarenal involvement limited to the cortex. In a second patient, a woman, aged 36, thrombosis of the femoral vein became evident on the ninth day after delivery, which took place five months before death. At the beginning of the fourth month before death, pigmentation of the skin was evident; the further course was that of a rapidly progressing Addison's disease. Both the cortex and medulla of each suprarenal gland were greatly reduced in amount and infiltrated by lymphocytes. The cortex contained dense bands of fibrous tissue and areas of necrotic detritus with cholesterol crystals. The veins of the suprarenal gland were transformed into solid cords as the result of the organization of the thrombus which had occluded each. To this case of vascular contracted suprarenal gland, with involvement of both medulla and cortex of each suprarenal gland and with symptoms of Addison's disease during life, the author adds two cases of unilateral thrombosis of the suprarenal vein with hemorrhagic infarction and rapidly ensuing death, for the purpose of illustrating the primary involvement of the medulla in this process and the degree to which the cortex may be destroyed. Next is presented a case of unusual interest in a woman aged 26 who was known to have had lymphogranulomatosis for three years prior to death. This clinical diagnosis was substantiated at necropsy. There was no active tuberculosis, but the medulla of each suprarenal gland was transformed into a calcified mass, over which there was a cortex of normal thickness and appearance. No accessory suprarenal tissue could be found. Symptoms of Addison's disease had been absent during life, and no pigmentation was noted at necropsy. The calcification of the medulla is interpreted as a healed tuberculous process. There follow two cases of generalized tuberculosis, without symptoms of Addison's disease during life; each patient had advanced tuberculous involvement of both suprarenal glands but unchanged aberrant suprarenal tissue.

In this interesting array of material, Kovács sees proof that complete destruction of the suprarenal medulla does not lead to death, that complete or almost complete destruction of the cortex is incompatible with life, that the sudden destruction of the cortex leads to death within a short time, that the more gradual destruction is associated with the syndrome of Addison's disease, and that aberrant cortical tissue, if present in sufficient amount, can protect the body against the ill effects of loss of the suprarenal cortex. He does not take the extreme view that loss of cortical function alone is responsible for the complete syndrome of Addison's disease. Loss of medulla alone would cause no symptoms warranting a diagnosis of Addison's disease. Loss of cortex alone would lead to this diagnosis because of the characteristic pigmentation, but the characteristic low blood pressure would be absent, as in his case of cytotoxic cortical atrophy. He further concludes that each kind of tissue, cortical and medullary, can function alone and need not necessarily have an interrelationship with the other. Objective observations, interpretations and deductions are well presented.

O. T. SCHULTZ.

AUTOTRANSPLANTATION OF BONE. R. DE JOSSELIN DE JONG and P. H. EYKMAN VAN DER KEMP, Beitr. z. path. Anat. u. z. allg. Path. **79**:268, 1928.

The authors are convinced that both surgical and experimental evidence indicates that autotransplantation of bone is uniformly much more successful than transplantation into another animal of the same species. Therefore, to study the fate of transplanted bone and the source of the newly formed bone they chose autotransplantation, using the rabbit as experimental animal. Bone with both periosteum and endosteum, bone with periosteum or endosteum alone and bone with neither periosteum nor endosteum was transplanted into the lumbar muscles of rabbits, and the material was examined at varying intervals after transplantation. Reimplantation of bone into the tibia and ulna was also tried. The bone corpuscles

of the transplanted bone degenerated, died and underwent lysis rapidly and completely. Substitution or rehabitation of the old bone did not occur, after either transplantation or reimplantation. The authors are emphatic in the statement that the living bone ultimately present has resulted only from the active proliferation of the osteogenic tissue of the periosteum, or endosteum. If proliferation of osteogenic tissue and regeneration of bone are to occur, infection, hemorrhage, and unnecessary mechanical insult must be avoided, and conditions must be such that a new vascular supply for the transplanted bone can be quickly provided. During the most active stage of proliferation of the osteogenic tissue, the newly formed tissue is osteoid. This is resorbed and replaced by normal bone as the proliferative activity recedes. Under the conditions of the experiments the proliferating tissues of the site of transplantation did not take part in the formation of new bone.

O. T. SCHULTZ.

CHANGES IN SYMPATHETIC GANGLIONS IN RELATION TO EXPERIMENTAL CHOLESTEROL ARTERIOSCLEROSIS OF THE RABBIT. F. DANISCH, Beitr. z. path. Anat. u. z. allg. Path. **79**:333, 1928.

Whether the arteriosclerosis of the aorta which occurs in rabbits that are fed a diet high in cholesterol is a process of degeneration or imbibition or is due in part also to mechanical factors has not been conclusively settled. The experiments of Danisch were designed to study the effects of changes in blood pressure on the production of cholesterol arteriosclerosis in the rabbit. Especial attention was paid to a microscopic study of the celiac ganglion, to determine whether changes here might help to cause arteriosclerosis through changes in blood pressure. Extirpation of the ganglion in normal rabbits caused wider fluctuations in blood pressure than normal, with a generally lower level. Intravenous injection of nicotine or epinephrine caused an earlier appearance of arteriosclerosis in animals that were given a diet high in cholesterol than in control animals. The ganglion cells of the celiac ganglion of animals fed cholesterol became degenerated and vacuolated. In more prolonged experiments some of the ganglion cells disappeared and were replaced by proliferated satellite cells. The changes noted are held to be purely degenerative and not inflammatory in character. Such changes are believed by the author to play a part in the development of the arteriosclerosis. In Danisch's experiments, 0.5 Gm. of cholesterol in linseed oil was fed daily by stomach tube. The highest levels of cholesterol in the blood varied in different animals and were usually reached after from ten to twelve weeks. Arteriosclerosis of the aorta began to appear when the level of blood cholesterol was between two and three times the normal amount. The article ends with eight pages of references to the literature.

O. T. SCHULTZ.

PATHOLOGIC HISTOLOGY OF GASTRIC MUCOSA. F. BÜCHNER and H. MORITZ, Beitr. z. path. Anat. u. z. allg. Path. **79**:400, 1928.

Büchner and Moritz made a detailed histologic study of the fundic portion of the stomach, paying especial attention to changes in the gastric channels (Magenstrasse). In three cases, heterotopia of the gastric mucosa to mucosa like that of the small intestine was noted; the change was limited, however, to the channels, the intervening mucosa being free. In two cases, a chronic ulcer was present at the pylorus, and in the third the scar of an ulcer was present at the same point. In one stomach heterotopic changes were present through the entire extent of the fundic mucosa, the histologic picture being that described by some writers in achylia gastrica. Eight stomachs showed no heterotopic changes; two of these were the seat of chronic pyloric ulcer. The limitation of the changes noted to the Magenstrasse in three of four stomachs which showed alteration of the heterotopic type lends support to the view that the mechanical irritation of food is a factor in the production of the changes, and may help explain the occurrence of gastric carcinoma at levels higher than is the rule for ulcer.

O. T. SCHULTZ.

ENDOCARDIAL POCKETS OF THE VENTRICULAR SEPTUM OF THE HEART. H. KAEWEL, Beitr. z. path. Anat. u. z. allg. Path. **79**:431, 1928.

Ribbert disagreed with the view of Schminke and others that the endocardial ridges and pockets sometimes seen on the ventricular septum of the heart are the result solely of mechanical action. The ridges and pockets occur most often in the left ventricle, usually on the upper part of the septum. They are crescentic or horseshoe-shaped, with the concavity directed upward. More rarely they occur on the under surface of the aortic segment of the mitral valve, and occasionally they are found on the septum near the apex of the left ventricle; in this case, the concavity is directed downward. The author made a histologic study of twenty-five hearts in which septal ridges and pockets were noted. In fifteen hearts, the aortic valve was insufficient, eight times as the result of syphilis of the aorta and in the remainder as the result of chronic aortic endocarditis. In the syphilitic patients, the inflammatory process had led to the formation of narrow channels between the bases of the aortic segments. The pockets occurred directly in the course of the blood stream which flowed backward through these channels. In the nonsyphilitic patients with aortic regurgitation, the backflow of blood was also held responsible. In ten cases, chronic mitral endocarditis was present. In two of these, the pockets were formed where fibrotic vegetations had rubbed against the septum. In the remaining eight cases, relative aortic insufficiency was held responsible. The author believes that in all the hearts studied by him mechanical factors alone are sufficient to explain the formation of the pockets. In none could he find any evidence that the process which led to the formation of the pockets was initiated as a true inflammation in the form of localized mural endocarditis, as postulated by Ribbert. As the result of the mechanical action of the backflow of blood, the endocardium undergoes localized thickening in the form of bands where the mechanical insult is greatest. Continuous action of the backward flowing blood stream transforms the ridge into a pocket. When the latter is situated near the apex and opens downward, the condition results also mechanically from the action of the regurgitating blood stream, which is directed upward at the apex in a parabolic curve and impinges against the lower portion of the septum.

O. T. SCHULTZ.

ACQUIRED BRONCHIECTASIS. H. SCHNEIDER, Beitr. z. path. Anat. u. z. allg. Path. **79**:466, 1928.

Schneider divides acquired bronchiectasis into an atrophic form, which is usually cylindric, and a hypertrophic form, which is usually saccular. Both types occur most frequently in the lower lobes of the lung and are often bilateral; involvement of an upper lobe alone is rare. In the atrophic form the bronchial wall is thinned in larger areas and dilatation results from intrabronchial air pressure. Secondary inflammation may lead to thickening of the wall. Without inflammation the wall may become sclerotic. In the hypertrophic form, the bronchial wall becomes thickened as the result of interstitial inflammation, which disrupts the muscle fibers. The inflammatory process usually occurs in localized areas, so that the dilatation is saccular. With more widespread involvement of the wall, this type may also become cylindric. In this type intrabronchial air pressure is also the main factor, although traction exerted by peribronchial fibrosis may play a part. The hypertrophic saccular form most often follows pneumonia. Traction by an adherent pleura is of little importance in the causation of bronchiectasis.

O. T. SCHULTZ.

LIPOID NEPHROSIS. K. LÖWENTHAL, Beitr. z. path. Anat. u. z. allg. Path. **79**:497, 1928.

The author claims that lipoid nephrosis has received inadequate attention in the German literature. He now adds three cases to the two that he previously reported and brings the literature, especially the American, down to the date of appearance of his communication. He reiterates his former conclusion that so-called

lipoid nephrosis is primarily a disease of lipoid metabolism and that the part of the kidney in the process is merely that of an excretory organ. Protein metabolism is also abnormal. Because of the purely secondary rôle of the kidney in the process, he deplores the use of the name lipoid nephrosis, and proposes protein lipoid diabetes as a preferable term.

O. T. SCHULTZ.

ORIGIN OF DUST CELLS IN THE SPUTUM. A. ROSIN, Beitr. z. path. Anat. u. z. allg. Path. **79**:625, 1928.

Since Arnold first described the phagocytic dust cells of the sputum in 1885, there has been lively controversy over the origin of these cells. Origin from alveolar epithelium, from septal capillary endothelium and from inwandering histiocytes has been claimed by various groups of investigators. Arnold himself described two types of dust cell, the larger one derived from alveolar epithelium and the smaller from lymphocytes. Rosin vitally stained guinea-pigs with pyrrhol blue and subjected them to mechanical, chemical and bacterial irritation of the lung. Mechanical irritation was produced by rarefied atmosphere, chemical by the fumes of nitric acid, and bacterial by setting up tuberculosis in the lungs. His results were negative after intravenous injection of the dye, no vitally stained cells appearing in the bronchial secretion. When the dye was introduced intratracheally, large vitally stained cells appeared in the bronchial secretion and could be seen in microscopic sections of the lungs. If the dye was in suspension, granules could be seen within the still attached and flattened alveolar epithelia within two minutes. If the stain was in solution the same cells were diffusely stained within twenty minutes; after a slightly longer period the dye within the cells was granular. The author concludes that the phagocytic cells of the sputum are alveolar epithelia.

O. T. SCHULTZ.

GIANT CRYSTALLOID CASTS IN THE KIDNEYS IN A CASE OF MULTIPLE MYELOMA. H. O. KLEINE, Beitr. z. path. Anat. u. z. allg. Path. **79**:678, 1928.

In a case of multiple myeloma, Kleine noted the occurrence of huge casts of peculiar composition in the dilated tubules of the kidneys. The casts consisted of an outer granular matrix which contained blood pigment and a doubly refractile crystalloid center. The urine contained Bence-Jones protein, but no mention is made of the presence of casts in the urine like those seen in the kidney. The presence of giant cells and leukocytes about the casts proves that the casts were not formed post mortem. Löhlein had described similar casts in the kidney in 1921, this being the only other report of such an operation, according to the author. The myeloma was of the plasma cell type. The mucosa of the stomach and small intestine was thin and atrophic. Amyloidosis was present in the internal organs. On the basis of the atrophic gastro-enteritis present in his case, the author builds a new theory of the pathogenesis of multiple myeloma. He supposes that incompletely digested protein is absorbed from the intestine, acts like parenterally introduced protein, and leads to amyloidosis. As a protective mechanism it also stimulates one or the other type of cell of the hematopoietic system to proliferation. By the action of cellular agglutinins formed locally, the newly formed hematopoietic cells are agglutinated and do not enter the circulation, thus forming the myeloma nodules.

O. T. SCHULTZ.

PATHOGENESIS OF TOLYLENEDIAMINE ICTERUS. H. EITEL, Beitr. z. path. Anat. u. z. allg. Path. **79**:700, 1928.

Earlier work on the icterus which follows the subcutaneous injection of tolylenediamine into dogs led to the conclusion that this is a purely hemolytic form of jaundice, due to the destruction of erythrocytes within the circulation by the poison. Rosenthal, Melchior and Licht claimed that extirpation of the liver prevented the development of icterus after tolylenediamine or caused its disappearance if already present; they concluded that the jaundice was wholly

hepatogenous in origin. They ascribed the icterus to early damage to liver cells, which thus became incapable of forming bile, and interpreted their experiments as strong support of the older doctrine of Minkowski and Naunyn that there can be no jaundice without a liver to elaborate bile. Kodama claimed that biliary thrombi are already present in the liver after seven hours of tolylenediamine intoxication, thus introducing resorption of bile as the chief factor in the causation of the icterus. Eitel's problem was to determine the relative importance of retention due to damage to the liver cells and of resorption due to hindrance of outflow in the mechanism of tolylenediamine icterus. His work was limited to intoxications of thirty hours' duration and longer. At thirty hours the blood serum gave a direct van den Bergh reaction and the urine contained both bile acids and bile pigment, indicating a resorption icterus rather than a hemolytic one. The liver contained many bile thrombi in the smaller interlobular ducts. Such damage to the liver cells as was present was interpreted as the result of bile stasis rather than of a direct action of the poison on the liver cells. Whether the primary factor was damage to bile duct epithelium or increase in the viscosity of the bile he could not determine. The icterus is of the resorption type and is due to hindrance of outflow through the presence of biliary thrombi.

O. T. SCHULTZ.

EARLY STAGES OF TOLYLENEDIAMINE ICTERUS. D. YUASA, Beitr. z. path. Anat. u. z. allg. Path. **79**:713, 1928.

Rosenthal, Melchior and Licht claimed that removal of the liver of dogs prevented the development of tolylenediamine icterus or caused its disappearance if already present. Kálláo asserted that the failure of bile formation in such experiments was due to the action of the dextrose necessary to maintain life in hepatectomized animals, and that bile pigment appears in the blood after removal of the liver. The present author paid especial attention to the early stages of tolylenediamine icterus. Unlike Kálláo, he found that dextrose does not inhibit bile formation, but contrary also to the observations of Rosenthal and his coworkers, he found that icterus occurs if the liver is absent. The degree of pigmentation of the blood serum is moderate in these animals, and bilirubinemia never becomes as marked as in animals with intact liver. The van den Bergh reaction, which theoretically should be of great help in determining what is happening during the early stages of the icterus, has little value because the reaction is interfered with by derivatives of tolylenediamine and also possibly pigments other than bilirubin, such as xanthochromes and precursors of bilirubin. During the early stages of the jaundice, in animals with intact liver, the thoracic duct lymph contains from two to three times as much bilirubin as the blood, indicating resorption of bile from the liver. Histologic examination of the liver at this early stage does not reveal the severe injury described by Rosenthal and his associates. Bile stasis can be detected in the intracellular bile canaliculi, and biliary thrombus formation has begun in the smaller interlobular ducts. The author concludes that in the beginning tolylenediamine icterus is hemolytic, but to only a slight degree; to a much greater degree it is obstructive and resorptive.

O. T. SCHULTZ.

HEALING PHENOMENA IN EXPERIMENTAL INFARCTION OF THE KIDNEY. U. SCHNAPAUFF, Beitr. z. path. Anat. u. z. allg. Path. **79**:781, 1928.

This is a contribution, by a pupil of Aschoff, to the long controversy between the latter and Ricker over Aschoff's neurovascular theory of inflammation. Since Ricker had interpreted the phenomena occurring in the early stages of renal infarction in support of his theory, Schnapauff caused infarction of the kidney in rabbits by ligating one of the branches of the renal artery. The resulting changes were studied at intervals, beginning immediately after the ligation and continuing until complete healing of the infarct occurred. In the earliest stages, the presence of free red blood corpuscles in the peripheral zone of the infarct was the result of

diapedesis through inactive, mechanically distended capillaries, and the leukocytic infiltration in this zone was due to chemotaxis. Healing occurs by the ingrowth of fibroblasts from the periphery and not as the result of any neurovascular reactions in the infarcted tissue. The interpretation of the observations, which are those familiar to all, is in the terms of cellular pathology, not in those of Ricker's neurovascular "Relationspathologie."

O. T. SCHULTZ.

PATHOLOGIC HISTOLOGY OF METRORRHAGIA. O. TERASAKI, Beitr. z. path. Anat. u. z. allg. Path. **79**:819, 1928.

The author made a histologic study of the endometrium in ninety-two cases of intermenstrual hemorrhage. The material consisted in greater part of curettings and in smaller part of extirpated uteri. He divides his material into three groups: hemorrhagic metropathy of Aschoff, inflammatory endometritis of infectious origin and senile apoplexy of the uterus. Most of his material fell into the first group and consisted of eighty-one cases. These he subdivides into a subgroup of twenty cases in which the glandular changes of the endometrium could be correlated with the normal menstrual cycle but were abnormal in the time of their occurrence in the cycle. The age in this group varied from 35 to 53 years. In the second subgroup of sixty-one cases, the endometrial glands were hyperplastic, but the hyperplasia is held to be not cyclic but permanent, a true glandular hyperplasia. In forty-five of these cases the age ranged from 43 to 62 years, in six it was from 20 to 43 years, and in ten less than 20 years. In the metropathies the chief change was vasomotor, a capillary instability, in the words of the author, which manifested itself by hyaline capillary thrombosis and capillary hemorrhage. Small areas of necrosis were also present, but these were not due to capillary thrombosis. The gitter fibrils of the superficial layer of the endometrium remained intact. The changes occurring in women at and past the menopause are the result of abnormal prolongation of the menstrual cycle and of abnormalities in the sequence of portions of the cycle. Occurring as a prolongation of the menopause or, in younger women, associated with glandular hyperplasia, the metrorrhagia is due to abnormal ovarian function or to disharmony between general metabolism and ovarian function. There were only four cases of true inflammatory endometritis. The endometrium was infiltrated by lymphocytes, often by plasma cells, and proliferation of stroma and capillary endothelium was noted. The senile apoplexy group consisted of seven patients whose ages ranged from 56 to 88 years. The endometrium was atrophic, and the walls of the arteries of the myometrium were greatly thickened. The hemorrhage is a terminal affair in the life of the woman and is the result of passive capillary hyperemia.

O. T. SCHULTZ.

FIBRO-ADENOMATOSIS CYSTICA MAMMAE. CARL SEMB, Acta chir. Scandinav. (supp. 10) **64**:1, 1928.

One hundred and forty-four cases of fibro-adenomatosis mammae were studied after the glands were dissected from fat, fascia, muscular and cutaneous tissues. Multiple parallel cut surfaces and from ten to twenty blocks stained by various methods were submitted to examination.

Fourteen cases were observed in men. Here the tumor varied considerably in size but was usually more or less round and elastic, and the line of demarcation from the surrounding fat tissue was not quite sharp. Microscopically, there were epithelial-lined passages which were surrounded by newly formed connective tissue, and outside the latter was fibrous connective tissue. Nowhere were there any glandular alveoli. This cellular new formation was regarded as a hypertrophic growth of connective and epithelial tissue rather than as an inflammatory process or genuine tumor. Only one case showed cyst-formation similar to that found in fibro-adenomatosis cystica in women.

Fibro-adenomatosis simplex (microcystica) presents large or small thickenings of firm consistency in the mammary gland. These thickenings may be local or diffuse, with grayish-white or whitish tissue which is more or less sprinkled with

reddish-gray specks that represent cystically dilated acini surrounded by young connective tissue; the interlobular supporting connective tissue is varied in quantity. The assumption is made that this is a simultaneous fibro-epithelial proliferation, because in early cases Semb never noted proliferation of epithelial tissue without corresponding changes in the connective tissue. If the new formation of glands continues further, small, medium, or larger lobules are formed with numerous epithelial-lined cavities. Fibro-adenoma differs in that it is a circumscribed tumor containing only epithelium and connective tissue. Fibrolipo-adenoma and adenoma are distinguished by a sharply demarcated connective tissue capsule. Chronic mastitis presents a well defined inflammatory process. Hypertrophy of pregnancy, especially in the early months, may resemble fibro-adenomatosis, but in the former there is regular epithelial proliferation with pronounced secretory activity, and the connective tissue recedes into the background. Menstrual or periodic changes in the mammae may simulate fibro-adenomatosis, but in the latter the changes are far more pronounced and irregular. Diffuse fibromatosis (Reclus, Schimmelbusch) is regarded as an advanced stage of fibro-adenomatosis.

Fibro-adenomatosis cystica simulates the microcystic form, but in addition there are multiple, macroscopically visible cysts. These cysts may be lined by ordinary mammary epithelium and represent dilated acini, or by pale epithelium which may form papilla-like structures; lastly, there may be adenomatous papillomas with vascular connective tissue in the stroma. The latter condition is found in dilatations or cystic extensions of the large milk ducts. Retention of secretion seems to play an important part in the formation of cysts larger than a pea, whereas the formation of smaller cysts is mainly due to active proliferation of epithelium.

Inflammatory changes in fibro-adenomatosis (microcystic) does not seem to be an etiologic factor. In the glands with large cysts the round cell infiltration is regarded as secondary. Abscess near the nipple was observed in nine breasts, but such inflammatory changes were regarded as recent. Xanthoma cells were frequently found in cysts, connective tissue cells and carcinoma cells. In all of 101 preparations there were 6 in which there was a previous mastitis; its occurrence in such a small number rules it out as an etiologic factor and should be regarded purely as a coincidence.

Adenomatous papillomas occurred in the milk ducts in 27 per cent of the cases as multiple and varying sized tumors in the later stages of fibro-adenomatosis cystica. Fibro-adenoma was not found in connection with the earlier stages of fibro-adenomatosis, but was noted in the late stages and arose as a proliferation of a single milk duct in the form of fibro-epithelial new-formations. In only 2 per cent of the cases of fibro-adenomatosis (microcystica) was there any atypical growth; in fibro-adenomatosis cystica, however, 24 per cent of the cases presented atypical infiltrating tumor tissue. The material seems to indicate that there is no definite relation between the local purulent inflammation in fibro-adenomatosis and the development of cancer. In bilateral fibro-adenomatosis cystica there is a tendency toward bilateral primary carcinoma of the breast in that it occurred in 9 of the 23 cases. The microscopic examinations were not complete, however, in all those reported. From his work Semb concludes also that carcinoma can have a multicentric origin. In two patients there were bilateral mammary metastases from the stomach, which demonstrated that the cancer tissue had no power of producing any secondary proliferation of a fibro-adenomatous character. In 40 per cent of the cases of carcinoma there were fully developed pictures of fibro-adenomatosis cystica, and in a further 40 per cent various less pronounced or special forms of fibro-adenomatosis were detected; the remaining cases did not show definite signs of fibro-adenomatosis.

The etiology of fibro-adenomatosis is not clear. Trauma may be a factor in some cases. The initial stages occur about the middle of the period of sexual maturity in women. The greater number of the more developed forms are found shortly before the climacteric, a smaller proportion during and after the climacteric. Unmarried women are affected relatively more frequently, and the lesion is more

frequent in nulliparae. The figures in relation to abortions and lactation are not adequate and therefore not of significance. The greatest majority of women had normal menstruation. There is no connection with senile involution of the mamma. The clinical picture, prognosis and treatment are also given.

RICHARD A. LIFVENDAHL.

Pathologic Chemistry and Physics

THE CONCENTRATION OF ACID AND BASE IN THE SERUM IN NORMAL PREGNANCY. H. C. OARD and J. P. PETERS, J. Biol. Chem. **81**:9, 1929.

Pregnancy may be accompanied by a decrease of approximately 5 per cent in the concentration of the basic cations available from the blood plasma. The authors offer no explanation of the decrease, but present an interesting and exhaustive discussion of its possible pathogenesis. The changes compensating for the decrease are described in detail.

ARTHUR LOCKE.

THE RELATION OF THE SERUM PROTEINS AND LIPIDS TO THE OSMOTIC PRESSURE. E. H. FISHBERG, J. Biol. Chem. **81**:205, 1929.

An extensive reduction in the concentration of protein available from the blood plasma, such as may accompany intensive hemorrhage, is followed by a compensatory lipemia, directed toward the restoration of a normal osmotic pressure.

ARTHUR LOCKE.

THE METABOLISM OF SULPHUR (CYSTINURIA). H. B. LEWIS and S. A. LOUGH, J. Biol. Chem. **81**:285, 1929.

A comparison of the quantities of cystine excreted by a patient with cystinuria during maintenance on cystine-poor and cystine-rich diets failed to indicate any impairment in the capacity of the subject to utilize this important amino-acid. The cystine voided during cystinuria would appear to be chiefly of endogenous origin.

ARTHUR LOCKE.

LIPID EXCRETION. W. M. SPERRY, J. Biol. Chem. **81**:299, 1929.

Dogs receiving an essentially lipid-free diet excrete a small but definite amount of lipids in the feces. The excreted lipids appear to be contained within the various cellular elements present: bacteria, desquamated epithelial cells, protozoans, etc., and do not necessarily represent the product of a secretion into the intestine.

ARTHUR LOCKE.

MICROSCOPIC AND X-RAY INVESTIGATIONS ON THE CALCIFICATION OF TISSUE. N. W. TAYLOR and C. SHEARD, J. Biol. Chem. **81**:479, 1929.

An optical study has been made of several types of calcification of tissue, including that of normal bone, of dental enamel and dentine, of rachitic bone, of bone low in phosphorus, of salivary calculus and of tuberculous lung. The conclusion is drawn that the solid inorganic phase consists essentially of very small crystals of apatite minerals of the general formula $3Ca_3(PO_4)_2.CaX_2$, in which X_2 ordinarily represents CO_3, F_2, $(OH)_2$, O, SO_4 and Ca, which may to some extent be replaced by Mg. The index of refraction may serve as a measure of the degree of calcification of dried tissues, being low for bones and high for dental enamel and in certain cases of pathologic deposition. It is probable that the index is determined by the relative amounts of inorganic crystal and organic material in the unit structure. Diffraction patterns of x-rays obtained by the powder method have been obtained for apatite, dental enamel, normal bone, salivary calculus, tuberculous pulmonary calcification and synthetic tricalcium phosphate. The similarity of the patterns indicates a similarity of crystal structure. The conclusion is in agreement with that based on the optical evidence.

AUTHORS' SUMMARY.

BLOOD AS A PHYSICOCHEMICAL SYSTEM (DIABETIC COMA). D. B. DILL, A. V. BOCK, J. S. LAWRENCE, J. H. TALBOTT and L. J. HENDERSON, J. Biol. Chem. **81**:551, 1929.

An enormous amount of critically evaluated data has been condensed into a monograph presenting a "synthetic" description of the physicochemical character and behavior of the blood during diabetic coma.

ARTHUR LOCKE.

THE ALKALINE RESERVE AND OXYGEN CAPACITY OF ARTERIAL AND OF VENOUS BLOOD. L. M. HURXTHAL, A. V. BOCK, J. H. TALBOTT and D. B. DILL, J. Biol. Chem. **81**:681, 1929.

In a series of normal subjects at rest and at work, and in another series of pathologic subjects only small differences were found between arterial and venous blood both with respect to carbonic acid capacity at a partial pressure of 40 mm. of CO_2 and with respect to oxygen capacity.

AUTHORS' SUMMARY.

DISTRIBUTION OF ELECTROLYTES IN HEMOPHILIC BLOOD. R. V. CHRISTIE, J. SENDROY and D. D. VAN SLYKE, Quart. J. Med. **22**:65, 1928.

The chloride and bicarbonate distribution ratios in hemophilic blood are within the range of these ratios in normal blood, but in the lower half. Also the mechanism governing the distribution of electrolytes between cells and serum of hemophilic blood appears to be normal. This study was made on specimens of blood from a young male negro who was a hemophilic and gave a family history characteristic of that disease.

N. ENZER.

CHRONIC MERCURIAL POISONING. A. HERTZ, Klin. Wchnschr. **8**:541, 1929.

Among thirty-five patients with amalgam teeth fillings, thirty-four were found to be eliminating mercury, a result in general agreement with published reports, although the percentage is somewhat higher. This is perhaps explained by the fact that in most cases more mercury is found in the stools than in the urine, and others have analyzed only the urine.

AUTHOR'S SUMMARY.

Microbiology and Parasitology

THE MONOCYTES IN ACTIVE TUBERCULOSIS. K. D. BLACKFAN and L. K. DIAMOND, Am. J. Dis. Child. **37**:233, 1929.

The degree of activity in tuberculosis is reflected in the peripheral blood of infants and of children. A high monocyte-lymphocyte ratio and the presence of epithelioid cells usually mean an active tuberculous infection. An increasing monocyte-lymphocyte ratio and the persistence of a high absolute monocyte count signify extension of the process. Reversal of the ratio (a fall in monocytes and an increase in lymphocytes) denotes healing lesions. In cases in which the diagnosis is questionable, a study of the blood by the supravital technic may lead to a correct diagnosis. When the diagnosis is established, supravital studies of the blood may be of prognostic value in indicating whether the lesion is progressing or undergoing regression.

AUTHORS' SUMMARY.

PULMONARY GANGRENE DUE TO SPIROCHETES AND FUSIFORM BACILLI. J. M. LEWIS and L. H. BARENBERG, Am. J. Dis. Child. **37**:351, 1929.

A case of pulmonary gangrene due to spirochetes and fusiform bacilli is reported in a child, aged 3 years. The presence of spirochetes and fusiform bacilli in smears taken directly from the larynx and from the fetid material obtained by lung puncture was instrumental in making the diagnosis. The importance of oral hygiene, prompt treatment of spirillar infections of the mouth and good nutrition in the prevention of fusospirochetal pulmonary gangrene is emphasized.

AUTHORS' SUMMARY.

VARICELLA COMPLICATED BY ACUTE NEPHRITIS: REPORT OF A CASE ASSOCIATED WITH STREPTOCOCCAL INFECTION OF THE TONSILS. E. RANKIN DENNY and B. M. BAKER, JR., Bull. Johns Hopkins Hosp. **44**:201, 1929.

A case of focal glomerular nephritis occurring early in the course of hemorrhagic varicella is reported. The onset of the nephritis, and the recovery from this complication paralleled the course of a complicating acute tonsillitis due to hemolytic streptococci, of the B type. The organisms isolated from the tonsils and urine had common cultural characteristics. During the acute stage of the nephritis, hemolytic streptococci of B type were found in the urine, while after recovery from the nephritis they disappeared from both the throat and the urine. It is suggested that the acute hemorrhagic nephritis in this case was associated not with hemorrhagic varicella but with the streptococcal infection.

AUTHORS' SUMMARY.

HETEROGENEITY OF STREPTOCOCCI FROM SPUTUM. SANFORD BURTON HOOKER and LILLIAN M. ANDERSON, J. Immunol. **16**:291, 1929.

Alpha streptococci, which predominate in minor respiratory infections, are of such extraordinary cultural and antigenic diversity even in the secretions of an individual patient, that they may almost certainly be excluded as primary pathogenic invaders; their rôle here as actual secondary agents of infection is probably very subordinate. Comparison of these organisms, which in plates give a fictitious impression of homogeneity, with the streptococci and other bacteria associated with more entitative types of disease, and whose actual cultural and antigenic homogeneity in the individual is strongly supported by the evidence available, has led to the formulation of this criterion of a primary microbic pathogen in a given individual: Multiple selections from the dominant colony type should show a high proportion of essentially indistinguishable strains. The changeable differences due to dissociative phenomena should be excluded. The beneficial reactions attributed to the "autogenous" vaccine treatment of bronchitis are probably not often mediated by a specific immunologic mechanism. A comprehensive classification of alpha streptococci cannot be achieved by current methods without an expenditure incommensurate with its probably limited value to the medical profession.

AUTHORS' SUMMARY.

REACTIONS OF GUINEA-PIGS TO VIRUS OF ENDEMIC TYPHUS FEVER. KENNETH F. MAXEY, Pub. Health Rep. **44**:589, 1929.

Blood from persons sick with the "endemic typhus" of southeastern United States injected into guinea-pigs produces a definite febrile illness, with recovery and subsequent immunity to reinoculation. The reaction of the guinea-pig appears to be identical with that produced by Mexican typhus, according to Mooser's description. It differs from that of the Old World typhus (1) in regard to the character of the fever curve, (2) in the relative rarity of the so-called typhus nodes in the histologic preparation of the brain, and (3) in the presence of an obvious and well defined scrotal lesion first described by Neill, in 1918, in Mexican typhus.

So far as the differences in the temperature curve and in the relative frequency of occurrence of typhus nodes are concerned, these might be explained as due to strain variation. In a study of thirteen strains obtained from cases in the same general locality in Poland, Hach found one strain in which, in spite of a very outspoken febrile reaction, the brain lesions were extremely hard to find. In another the temperature elevations were relatively slight, although the period of incubation and duration of the fever were essentially the same as in other strains.

On the other hand, the involvement of the scrotum is much more striking and extensive than has been observed or described in guinea-pigs inoculated with Old World typhus. When this obvious involvement was first encountered in a strain obtained from a case in Montgomery, Ala., in 1925, it was thought possible

that it might be due to a secondary or contaminating infection. Since that time the same condition has been present in three other strains which have been successively established from cases in Montgomery, Ala., Savannah, Ga., and Wilmington, N. C. It was observed by Dr. William Allan in a strain from a case in Charlotte, N. C. It has been constantly associated with the presence of the virus and not with other infections in guinea-pigs. It has not been observed during the past two years in guinea-pigs from the same stock which have been inoculated with two strains of Old World typhus, though much less extensive histologic changes of a similar nature occur.

These observations have been so consistent that it seems to be established that the obvious involvement of the scrotum and the rarity of brain lesions are characteristic of the endemic typhus virus in guinea-pigs as they are of Mexican virus. The demonstration of rickettsia-like organisms in the epithelial cells of the tunica brings additional evidence as to their identity. It appears, therefore, that a North American strain of typhus can be recognized and distinguished from Old World typhus, though the two be closely related immunologically.

The conclusion may be drawn that the disease which is endemic in our eastern seaports, Wilmington, N. C., Charleston, S. C., Savannah, Ga., Jacksonville, Fla., belongs to the typhus group, but is not dependent on importation from across the sea. This disease has a common origin with the typhus of Mexico, even though transmission be effected by some agent other than that generally recognized for this disease, namely, the louse.

AUTHOR'S SUMMARY.

THE EXHAUSTION OF MEDIA IN BACTERIAL CULTURE. J. C. BROOM, Brit. J. Exper. Path. **10**:71, 1929.

The power of fruit juice in aiding the regrowth of an organism on an agar slope on which the organism has already been grown for some days is dependent, not on its vitamin content, but on the presence of carbon compounds which the organism can assimilate. The inhibition of the growth of one bacterium by another may be caused by a deficiency of available carbon due to the original growth. This explains why bacteria with greater powers of fermentation inhibit those which are less active in this respect.

PEARL ZEEK.

THE INFLUENCE OF COMPLICATIONS ON THE COLLOID LABILITY IN PULMONARY TUBERCULOSIS. L. HANTSCHMANN and M. STEUBE, Beitr. z. Klin. d. Tuberk. **70**:536, 1928.

In 200 patients with pulmonary tuberculosis, the sedimentation rate and the protein fractions were determined. The deviations of the latter are not proportional with the sedimentation rate. Extrapulmonary tuberculosis and inflammatory diseases increased the sedimentation rate and the globulin fraction beyond the degree that could be expected on account of the pulmonary lesion. Circulatory disorders, liver diseases, endocrine and constitutional disturbances caused at times a relatively decreased sedimentation rate.

MAX PINNER.

THE COURSE OF GENITAL TUBERCULOSIS IN THE PREGNANT, PUERPERAL AND ALLERGIC ANIMALS. J. GRANZOW, Beitr. z. Klin. d. Tuberk. **70**:548, 1928.

In all these experiments tubercle bacilli were injected into one horn of the guinea-pig uterus. It was found that uterine lesions developed in 6 per cent of normal uteri, in 28 per cent of pregnant uteri, in 45 per cent of puerperal uteri, and in 50 per cent if a subcutaneous primary infection had preceded the intra-uterine infection. The survival period was shortened in animals which were in the pregnant or the puerperal stage. The uterine lesions produced by local infection may occur anywhere within the uterine cavity. The peripheral layers are more frequently diseased than the central layers. The histologic picture of uterine tuberculosis is frequently atypical. Following an intra-uterine reinfection,

acute endometritis may develop. After uterine infection a number of nonspecific alterations may occur in this organ. They may be degenerative, inflammatory, disturbances of the circulation or marked atrophy of the whole organ. An ascending tuberculosis of the tubes was never observed, neither were the ovaries infected. Pregnancy is almost always interrupted by uterine infection. This mode of infection almost always produces sterility. Coincident with uterine lesions, the regional lymph glands are almost always diseased. If no uterine lesions are found the regional lymph glands may still be tuberculous. In puerperal animals the entire lymphatic system shows more pronounced lesions than in normal animals, while the lungs appear less affected.

MAX PINNER.

THE PATHOGENESIS OF TUBERCULOUS MENINGITIS IN CHILDHOOD. D. VON WANGENHEIM, Beitr. z. Klin. d. Tuberk. **70**:670, 1928.

The frequency of tuberculous meningitis in children at the age of from 1 to 3 years is probably due to the fact that at this age extensive caseation of bronchial lymph glands is particularly frequent. Measles, whooping cough, clinically active tuberculosis and trauma do not seem to play an important rôle in the development of the disease. Occult tuberculosis seems to be more important. Vaccination and heliotherapy are some times suggestive as causative factors. In about 50 per cent of the patients, the tuberculin reaction was positive eight days before death, which proves that a decrease of allergy is not a necessary condition for the development of generalization. Extrafamilial infection is twice as frequent as intrafamilial. Primary pulmonary foci were found in 95 per cent of the cases. Their localization does not seem to play a significant rôle in the development of meningitis. The focus from which generalization occurs is most frequently a caseated focus in bronchial lymph nodes. In 12 per cent of the cases, solitary tubercles in the brain were found. Intima tubercles in the pulmonary veins are rare. Their localization and structure argue against Weigert's theory, and favor the opinion of Liebermeister and Huebschmann, according to whom generalization occurs, not by the rupture of a vascular focus, but by bacillemia maintained by an extravascular focus.

MAX PINNER.

THE PATHOLOGIC ANATOMY OF PULMONARY INFILTRATIONS. H. RUBINSTEIN, Beitr. z. Klin. d. Tuberk. **70**:773, 1928.

A child was diagnosed as having an interlobar empyema. A rib resection was done and the pleural cavity was opened, but no exudate was found. A solid subpleural nodule was felt in the right middle lobe. Small pieces were excised for histologic diagnosis. After the operation, the child made a good recovery and the roentgenologic shadows disappeared almost completely. Both the clinical course and the histologic studies showed that the process was a tuberculous infiltration of the pulmonary tissue. The sections showed densely infiltrated lung tissue, the presence of tubercle bacilli, small necrotic foci, giant cells and diffuse proliferation of connective tissue. These observations show, too, that tuberculous infiltrations may be absorbed to a large extent.

MAX PINNER.

ACUTE DIFFUSE ENCEPHALITIS IN STREPTOCOCCUS ENDOCARDITIS. P. KIMMELSTIEL, Beitr. z. path. Anat. u. z. allg. Pathol. **79**:39, 1928.

The term endocarditis lenta should be limited to those cases of subacute bacterial endocarditis due to *Streptococcus viridans*. This form is characterized by infrequent occurrence of septic emboli which go on to abscess formation. In a few cases the presence of embolic abscesses within the brain has been reported. Purulent meningo-encephalitis of the brain has also been described. The author records eleven cases of subacute bacterial endocarditis due to *Streptococcus viridans*, in which there was diffuse involvement of the brain without abscess formation. The process was in part a degenerative one, consisting of areas of softening, which

the author considers ischemic in origin, and in part of a reactive inflammatory nature characterized by glial proliferation. The author believes such a diffuse nonpurulent encephalitis to be a not infrequent terminal process in viridans endocarditis.

O. T. SCHULTZ.

POSTVACCINAL ENCEPHALOMYELITIS. P. SCHÜRMANN, Beitr. z. path. Anat. u. z. allg. Pathol. **79**:409, 1928.

Although postvaccinal encephalomyelitis has shown a decided increase since 1922 in England and Holland, where the condition has been carefully studied histologically, the author claims that there are no previous reports of histologic studies in the German literature. The two cases studied by him occurred in children, aged 8 years and 18 months, respectively. The characteristic change noted by him was a zone of demyelinization about the dilated veins, usually at the junction of white and gray matter. Proliferation of glia was also noted. The changes occurred in both brain and cord. In the older child, in whom the vaccination was complicated by numerous furuncles in the axillae and on other parts of the body, there was infiltration by lymphocytes and large mononuclear cells about some of the veins, in addition to the more characteristic demyelinization. In his discussion of the nature of the process, the author does not accept the view of Luksch that the involvement of the nervous system is directly due to the vaccine virus. Perhaps the latter prepares the ground in susceptible persons for changes which are the result of nonspecific toxins. Schürmann holds the encephalomyelitis following vaccination to be identical histologically with that which may follow measles.

O. T. SCHULTZ.

THE RELATION OF OXIDIZING SUBSTANCES IN BACTERIA AND YEASTS TO CELLULAR OXIDASES. W. LOELE, Virchows Arch. f. path. Anat. **267**:733, 1928.

The author studied the granules that could be demonstrated in bacteria with paraphenylendiamine, with or without α-naphthol. *M. catarrhalis* could be readily distinguished from other throat organisms by this reaction. Oxidizing substances were shown in yeast cells by means of the peroxidase reaction with benzidine. The granules appeared variously colored, depending partly on the age of the culture, and were either diffuse or localized in some structure of the cell. The oxidizing substances in bacteria were bound to various structures, mostly to lipoids. The presence of oxygen was essential to the formation of these substances, but they could be formed only by certain types of organisms. The presence of iron appeared to influence favorably the oxidase reaction in yeast cells. The oxidases were found to be complex bodies, with oxidizing, lytic and pigment-forming properties, possibly related to nucleolar substance. Similarity was shown between bacterial and cellular oxidases in several respects.

B. R. LOVETT.

TUBERCULOSIS INFECTION AND TUBERCULOSIS VACCINATION. J. HEIMBECK, Ztschr. f. Tuberk. **52**:378, 1928.

Pirquet reactions were done on more than 2,000 persons of all ages in Norway. The results showed that only a minority of children was infected with tuberculosis, and that the most important period of infection must be between 15 and 20 years of age. These studies led to the conclusion that tuberculous disease at adult age is usually a direct consequence of the primary infection, and is not caused by a latent childhood infection. A latent childhood infection seems to afford a fair protection against later infections. A number of adults and children with negative Pirquet reactions were given injections subcutaneously with B.C.G. vaccine. They developed a tuberculin allergy. Observations on vaccinated and nonvaccinated nurses led to the conclusion that this B.C.G. allergy affords the same immunity as a benign natural infection.

MAX PINNER.

Immunology

HYPERSENSITIVENESS TO DIPHTHERIA BACILLI. JAMES M. NEILL, WILLIAM L. FLEMING and EMIDIO L. GASPARI, J. Infect. Dis. **44**:150, 1929.

In this study of the skin reactions to injections of diluted diphtheria culture filtrate, a group of 1,350 adults was tested with injections of 8 x 10^{-4} cc. of heated (80 C.) filtrate, and of the same amount of broth culture medium. Immediate reactions that could be referred to the diphtheria bacterial derivatives occurred in only four persons, 0.3 per cent of the group. Reactions to injection of the test dose of diluted broth, on the other hand, were common, significant ones being observed in 18 per cent of the group. Most of the responses to the injection of diluted broth could be referred to actual constituents of broth, but some reactions were apparently due to trauma alone. A general outline is given by which the skin reactions to intradermal injections of the whole bacterial filtrate may be distinguished.

AUTHORS' SUMMARY.

THE PROTEINS OF EGGWHITE. LUDVIG HEKTOEN and ARTHUR G. COLE, J. Infect. Dis. **44**:165, 1929.

Tests made with the precipitin reaction indicate that crystallized ovalbumin, when subjected to putrefactive processes, is not converted into conalbumin. It has also been shown that such a putrefying solution of ovalbumin loses its power to react with its specific antiserum even while it still contains a considerable amount of coagulable protein.

AUTHORS' SUMMARY.

IMMUNE REACTIONS TO ACID TREATED BACTERIA. ORAN I. CUTLER, J. Infect. Dis. **44**:203, 1929.

Bacteria treated with chemicals appear to lose the ability to incite antibody production in close proportion to their loss of power to produce immunity. When immunity to live typhoid bacilli was demonstrated, agglutinins for the organisms were also found, at least in low titer. Bacteria which are not completely destroyed by chemicals with which they are treated may be changed so that new antigens are formed, to which rabbits respond by the production of antibodies specific for the altered bacteria. Antibodies formed for typhoid bacilli treated with nitric acid, which were different from those formed for live organisms, were not demonstrated to be bactericidal for live bacteria. The antibodies formed for typhoid bacilli treated with second-normal acid appear to be the same whether nitric, hydrochloric, sulphuric or acetic acid is used.

AUTHOR'S SUMMARY.

PASSIVE TRANSFER OF HYPERSENSITIVESS TO DIPHTHERIA BACILLI. JAMES M. NEILL and WILLIAM L. FLEMING, J. Infect. Dis. **44**:224, 1929.

The three types of skin reaction to diphtheria bacterial derivatives are differentiated in this paper by passive transfer experiments. The capacity for the immediate hypersensitive reaction to heated diphtheria filtrate was transferred to 61 to 103 persons by the Prausnitz-Küstner technic; the capacity for the delayed or pseudo reaction to the same heated filtrate failed of transference. Serum from persons without the pseudo reaction had no neutralizing effect when previously injected into the skin of persons with pseudo reactivity, serum from a person with a negative Schick reaction transferred local antitoxic immunity to skin areas of persons with positive Schick reactions, as indicated by neutralization of toxin injected two days after introduction of the serum.

The success or failure of the Prausnitz-Küstner technic to transfer to local skin areas the types of antidiphtheria immunity represented by the three different skin reactions is illustrated. The results showed that active antidiphtheria immunity had no relation to a person's response in the passive transfer of the immediate skin reaction to the culture filtrate of the same bacteria.

AUTHORS' SUMMARY.

ANTICOMPLEMENTARY POWER OF HEPARIN. ENRIQUE E. ECKER and PAUL GROSS, J. Infect. Dis. **44**:250, 1929.

Heparin inhibits hemolysis in vitro in the hemolytic system. This is the result of action on complement rather than on cells. The heparin-inactivated complement can be reactivated by the addition of heat-inactivated human or guinea-pig serum. Thus, it is inferred that the action of heparin is on the third or fourth component of the complement. The facts that NH ammonia-complement reactivates heparin-inactivated complement and that guinea-pig serum inactivated by cobra venom fails to reactivate heparin-inactivated complement point to the conclusion that the action of heparin is on the third rather than the fourth component. The anticomplementary power of heparin is not clearly demonstrable in vivo, in spite of highly anticoagulant properties. This fact, together with the demonstrated influence of the chlorides of calcium, magnesium and lithium, indicates that the anticomplementary and anticoagulant properties of heparin depend on separate mechanisms. The experiments plainly show that heparin operates on complement, but ancillary action on amboceptor cannot be excluded.

AUTHORS' SUMMARY.

EFFECT OF MULTIPLE INJECTIONS OF DIFFERENT MATERIALS ON THE RETICULO-ENDOTHELIAL SYSTEM AND ON THE IMMUNITY RESPONSE. KATHARINE M. HOWELL and DOROTHY A. BEVERLEY, J. Infect. Dis. **44**:298, 1929.

The histologic examination of tissue, after the injection of multiple nonprotein foreign material, suggests the probability that the proliferation of reticulo-endothelial cells is so stimulated and so rapid that complete blockade of the reticulo-endothelial system cannot be attained.

AUTHORS' SUMMARY.

HYPERSENSITIVENESS TO DIPHTHERIA BACILLI AND RAGWEED POLLEN. WILLIAM L. FLEMING and JAMES M. NEILL, J. Infect. Dis. **44**:308, 1929.

The investigation consisted of a quantitative correlation of the responses of a group of people to ragweed pollen extract, in skin locally sensitized by ragweed hypersensitive serum, with the responses of the same persons to diphtheria culture filtrate in skin locally sensitized by diphtheria hypersensitive serum. Proper quantitative relationships between serum and test substance were established by preliminary experiments. The final tests for comparison were made on sixty-four persons. When the pollen-antipollen and bacterial-antibacterial systems were properly adjusted, the skin response of each person to one antigen was approximately the same as his response to the other; in most cases, they were identical. The quantitative correspondence in the individual transfer responses to the bacterial and nonbacterial antigen is illustrated. The results were discussed both from the standpoint of their significance in the study of diphtheria bacterial hypersensitiveness and from the standpoint of their theoretical interest in the study of hypersensitiveness in general.

AUTHORS' SUMMARY.

HISTAMINE IN RELATION TO CUTANEOUS HYPERSENSITIVENESS. JAMES M. NEILL, WILLIAM L. FLEMING and LURLINE V. RICHARDSON, J. Infect. Dis. **44**:321, 1929.

The individual variations in the response of normal skin to histamine were studied in thirty persons who had previously shown individual differences in responsiveness to antigens injected into specifically sensitized skin. Differences in reactivity to histamine were exhibited by the normal skin, but there was no correlation between the degree of responsiveness of the normal skin to histamine, and the responsiveness of the sensitized skin of the same person to injection of specific antigens. This lack of correlation is discussed from the standpoint of the usually accepted explanation of the mechanism of hypersensitive reactions.

AUTHORS' SUMMARY.

ANTI-VACCINAL SERUM. C. H. ANDREWES, J. Path. & Bact. **32**:265, 1929.

Generalized lesions appeared on the skin of 79 per cent of rabbits inoculated intradermally with a testicular strain of neurovaccine. This generalization could be prevented by giving comparatively small doses (3 cc.) of immune serum intravenously. Generalized lesions always appeared on the skin of rabbits inoculated intravenously with more than 500 skin-infecting doses of neurovaccine. Here also generalization could be prevented by giving intravenous serum before or mixed with the virus. With the serums used, approximately 1 cc. was necessary for every 1,000 m. i. d. of virus. Fifty-five per cent of the rabbits in which the serum prevented generalization were found on subsequent test to have developed an active immunity. Serum which reaches the tissues five minutes before the virus is far more effective than when the virus is five minutes ahead of the serum. This is most easily shown by "local passive immunity" experiments in the rabbit's skin.

AUTHOR'S SUMMARY.

THE SCHICK REACTION AND CIRCULATING ANTITOXIN. A. T. GLENNY and HILDA WADDINGTON, J. Path. & Bact. **32**:275, 1929.

Tolerance for diphtheria toxin may be determined by the intracutaneous injection of multiples of the Schick dose. Large reactions may be avoided by the use of toxins so chosen that the specific toxicity of the dilutions used is the same as that of the routine Schick dilution but the combining power is greater. A concentration of antitoxin in the blood of 1/250 unit per cubic centimeter of serum corresponds to the Schick negative level in guinea-pigs. In passively immunized guinea-pigs, this correspondence is not reached until equilibrium is reached between the circulation and tissues many hours after the injection of serum.

AUTHORS' SUMMARY.

IMMUNIZATION AGAINST CHICKENPOX. F. BENINI, Riv. di clin. pediat. **26**:824, 1926.

Benini gives his experiences with vaccination against chickenpox. He employed vaccination in forty cases, in twenty-seven using the scarification method and in thirteen intradermal inoculation with the lymph. He concludes that vaccination against chickenpox, if carried out with great care, is absolutely harmless. Prophylactic vaccination makes it possible to limit the spread of the disease. The best results are secured by employing the intradermal route. If chickenpox were always the mild disease that it is commonly, vaccination might be said to have chiefly an academic or scientific interest, but the fact is that the disease is not always benign but often takes on a nature dangerous to life, particularly in hospitals and gouttes de lait in which the patients are in a condition of lessened resistance.

ALLERGY OF THE TUBERCULOUS RABBIT AFTER SUPERINFECTION OF THE MESENTERY, CONJUNCTIVA AND CUTIS. H. H. KALBFLEISCH, Beitr. z. Klin. d. Tuberk. **70**:465, 1928.

In the first communication (*Beiträge zur pathologischen Anatomie und zur allgemeinen Pathologie* **78**:187, 1927), it was shown that the injection of tubercle bacilli causes local alterations in the circulation which vary with the amount of bacilli injected. These alterations secondarily cause changes in the tissue. The particularities of these processes are independent of the specific type of stimuli, but they are dependent on the degree of the stimuli. The same as in the first paper, an attempt is made in this study to prove the correctness of Ricker's "Relationspathologie" on the special example of tuberculous infection and reinfection. It is impossible, in a brief abstract, to report the author's experiments and arguments. Some of his most important conclusions are as follows: The processes caused by a tuberculous reinfection show certain deviations from those of a primary

infection only in animals with far advanced tuberculosis and not in animals with slight lesions. These deviations are caused by changed irritability of the nerves of the circulatory system. Far advanced tuberculous animals exhibit this changed irritability not only toward a specific reinfection but toward other stimuli as well (epinephrine). Therefore, the term "allergy" loses its meaning and should (with the term, tuberculosis immunity) be dropped from discussions of tuberculosis. The so-called "allergic reaction" indicates only severe disease. The local reaction of tuberculous superinfection is nonspecific. The "Koch phenomenon" is not an immunity reaction. Infection and reinfection, each being a nonspecific process, are distinguished only by circulatory alterations of varying degree.

MAX PINNER.

GLANDULAR REACTIONS FOLLOWING INJECTIONS OF OLD TUBERCULIN IN TUBERCULOSIS IN GUINEA-PIGS. K. G. LEDERMANN, Beitr. z. Klin. d. Tuberk. **70**:627, 1928.

In experimental tuberculosis of guinea-pigs, injections of tuberculin produce frequently an acute swelling of lymph glands particularly of those near the site of injection. This reaction is at times more sensitive, but less specific than the skin reaction. After repeated injections of tuberculin, the glandular reaction increases in intensity. Macroscopically unaltered glands react more frequently than macroscopically diseased glands.

MAX PINNER.

ACTION OF TUBERCULOUS ANTIGEN AND ANTIBODY ON A SURVIVING VASCULAR PREPARATION OF TUBERCULOUS GUINEA-PIGS, AND ITS PRACTICAL SIGNIFICANCE. U. RABBIOSI, Beitr. z. Klin. d. Tuberk. **71**:229, 1929.

Surviving vascular preparations from tuberculous guinea-pigs reacted with a vascular dilatation on perfusion with bacilliary products such as bacillary emulsion or old tuberculin, while similar preparations from normal guinea-pigs reacted with a contraction. Serum from tuberculous patients, too, produced a vascular dilatation, but not, as a rule, in preparations from normal guinea-pigs. The author believes that the technic, which is described in detail, may be adapted for practical diagnostic purposes.

MAX PINNER.

LOCAL IMMUNIZATION AGAINST TUBERCULOSIS. K. W. CLAUBERG, Beitr. z. Klin. d. Tuberk. **71**:263, 1929.

Guinea-pigs were given intrapulmonary injections of various preparations of tubercle bacilli. Some time later they were infected by the same route with virulent tubercle bacilli. It appeared that some degree immunity had been produced.

MAX PINNER.

THE EFFECT OF ROENTGEN RAYS ON SPECIFIC IMMUNE BODIES. ALEXANDER LUSZTIG, Centralbl. f. Bakteriol. **105**:142, 1928.

Lusztig finds that exposure of animals to roentgen rays may have various effects on antibody production, depending on the intensity of the radiation, the antigen used and the time of application of the rays with respect to the time of injection of the antigen.

PAUL R. CANNON.

THE PROPERTIES AND MODE OF ACTION OF ANTHRAX-IMMUNE SERUM. ALFRED PETTERSSEN, Centralbl. f. Bakteriol. **106**:294, 1928.

Petterssen asserts that anthrax-immune serum contains agglutinins, precipitins and complement-fixing antibodies but no bacteriolytic or opsonic ones. He believes, on the basis of experiments described in this paper, that in the animal body the anthrax bacilli form negatively chemotactic substances, these being particularly concentrated in the edema fluid. Immune serums contain substances which

neutralize these negatively chemotactic materials, thus allowing leukocytes to infiltrate and phagocytize the organisms. The virulence of the bacilli, then, depends on their ability to form these leukocyte-repelling substances; consequently, the virulence can be increased only by animal passage.

PAUL R. CANNON.

THE SIGNIFICANCE OF THE RETICULO-ENDOTHELIAL APPARATUS IN INFECTIONS. J. L. KRITSCHEWSKI and L. SCHWARZMANN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **56**:322, 1928.

The reticulo-endothelial system does not act, or only to a minor extent, as a protective apparatus in infections with *Trypanosoma gambiense*. There was no evidence of any protective action in *Schizotrypanum cruzi* and *Spirochaeta morsus muris*.

W. C. HUEPER.

THE ANTIVIRUS OF BESREDKA IN EXPERIMENTAL STREPTOCOCCUS INFECTIONS. H. DOLD and H. R. MÜLLER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **56**:347, 1928.

The growth inhibiting action of sterile filtrates of old, repeatedly inoculated bouillon cultures (antivirus of Besredka) can be explained satisfactorily by exhusation of the culture medium and the accumulation of specific inhibitory metabolic products. The inhibitory quality of *Streptococcus antivirus* is heat resistant. It is almost atoxic for rabbits. Rabbits could not be immunized by injections of *Streptococcus antivirus* against fatal streptococcus infections (virulency type III). The local reaction could be decreased and the life lengthened by several days through preceding intracutaneous injections with antivirus. The same results, however, were obtained by injections of bouillon and physiologic solution of sodium chloride. Similar results were seen in streptococcus infection of the virulency type II thus treated. Simultaneous injections of antivirus, bouillon or physiologic solution of sodium chloride, respectively, and infecting streptococci (virulency type II) had an unfavorable effect evidenced by the more marked local reaction and the lengthening of the disease. The results obtained by intracutaneous injections or local applications on infected lesions for therapeutic purposes gave varying results. Failures were frequent. As the antivirus acts as an inflammation-producing agent the best results were obtained by its prophylactic use twenty-four hours preceding the infection. The results were less reliable and less marked if the antivirus was used twenty-four hours after infection. The inflammation-producing action of injections of antivirus, as well as of bouillon and physiologic solution of sodium chloride, are due to the resulting injury of the tissue. The authors deny the existence of an antivirus which, according to Besredka, represents a split product of bacteria with a special affinity to the cells of the skin.

W. C. HUEPER.

THE NORMAL AND NONSPECIFICALLY ALTERATED BACTERICIDAL POWER OF THE SERUM. W. PFANNENSTIEL, Ztschr. f. Immunitätsforsch. u. exper. Therap. **56**:389, 1928.

The bactericidal power of the serum could be lowered in test tube experiments by various means (heat, irradiation with ultraviolet rays, p_H changes, changes in mineral content, addition of absorbents, etc.) due to changes in the colloidal status of the proteins and lipoids. The physicochemical status of the serum in the animal decides its bactericidal power. Changes in its content of mineral and dissolved cellular substances are effected by leukocytes, histiocytes, platelets and probably also cells of the reticulo-endothelial system. The physicochemical and chemical structure, especially lipoid content, of the bacterial to be tested is also important in regard to the bactericidal action. Gram-positive bacteria, if susceptible to the bactericidal serum, succumb to it more easily than gram-negative ones. The normal

bactericidal quality against typhoid bacteria varies with different animals and in the individual with the different physiologic and pathologic conditions. Changes in the bactericidal "serum-status" can be produced in vivo by various nonspecific means resulting in disturbances of the physicochemical balance of the blood and alterations of the cellular colloids, especially of the reticulo-endothelial system and the autonomous vegetative system. Changes in the bactericidal power, which may be marked, are usually only temporary and of short duration. An increase of longer duration after injections is apparently rare and follows only substances which are not readily excreted as metals, rare earths, acetylsalicylic acid and the like. Alimentary influences, especially the introduction of vitamins, and pregnancy may produce long lasting increases of the bactericidal quality of the serum. Variations depend apparently on the exchanges of substances between the blood and the tissues, in which the reticulo-endothelial system plays an important part. Vascular dilatation effects an increase, vasoconstriction a decrease of the bactericidy due to changes in the permeability of the vascular wall. Decrease of the dispersion of the blood colloids increases the bactericidal power, while it is lowered by increase of the dispersion. The increase of calcium magnesium and potassium with simultaneous decrease of sodium in the blood results in an increase of the bactericidal qualities; the increase of sodium with simultaneous decrease of calcium and potassium produces a decrease of them. Weak acids increase the bactericidal qualities, weak bases have no effect. Incompensated acidosis, as present after parenteral injections of proteins, diminishes the bactericidal power. The subsequent excessive compensatory activity of the cells overcomes this injurious effect. Fever increases the bactericidy. The poisonous effect of metals, especially arsphenamine and acetylsalicylic acid, on the capillaries results in an increase of the bactericidal qualities. The sterilizing effect of chemical therapeutics depends also on the active participation of the cells, especially those of the reticulo-endothelial system.

W. C. HUEPER.

IMMUNOLOGIC SPECIFICITY OF SERUM CONSTITUENTS SEPARATED BY AN "ELECTRO-OSMOTIC" METHOD. R. OTTO and K. IWANOFF, Ztschr. f. Immunitätsforsch. u. exper. Therap. **57**:19, 1928.

Serum fractionated by an "electro-osmotic" method gave results in general conformity with those reported in the literature for serum fractionated by the usual methods. The globulin and albumin fractions proved specific in active anaphylaxis experiments; euglobulin and pseudoglobulin usually, but not always, could be distinguished from each other; the soluble and insoluble albumin fractions were less specific. Species specificity obtained in passive anaphylaxis experiments with the antiserums of most of the serum fractions.

R. C. AVERY.

ANTIGENICITY OF LIPOIDS. S. JERMOLJEWA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **57**:102, 1928.

Ether extracts of egg yolk possessed antigenic properties; cholesterin and lecithin did not. Activation with hog serum changed cholesterin and lecithin from haptines to typical antigens. Separate injection of serum and the lipoids gave negative results.

R. C. AVERY.

A BIOLOGIC HOMOLOG OF HUMAN SPERMATOZOA. N. J. ROSANOW, Ztschr. f. Immunitätsforsch. u. exper. Therap. **57**:164, 1928.

The antiserums of rabbits and women immunized with the spermatozoa of other animals (ox, horse, hog, dog, cow, rabbit, guinea-pig) checked the motility of the antigen-spermatozoa, but had no influence on human spermatozoa. In contrast, the serum of rabbits immunized with ape spermatozoa proved hetero-spermatoxic to human spermatozoa.

R. C. AVERY.

THE RICKENBURG-BRUSSIN REACTION IN HUMAN RELAPSING FEVER. W. M. ARISTOWSKY and E. P. SCHAECTER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **57**:347, 1928.

The Rickenburg-Brussin reaction (adhesion of spirochetes to blood platelets) observed by others with serum of infected animals was obtained with serum from a patient locally infected with a culture of *S. recurrensis*. The reaction was given by either serum or plasma from blood drawn on the day following the fall in temperature; with their patient high serum dilutions (1 : 1,000) were effective. The blood platelets used in the test must be obtained from a healthy rat, guinea-pig or rabbit, but not from man. They suggest that their results indicate that the antibodies responsible for the adhesion phenomenon are identical with spirochetolysins.

R. C. AVERY.

ISOLATION OF GROUP SPECIFIC AGGLUTINOGENS OF HUMAN ERYTHROCYTES. C. HALLAUER, Schweiz. med. Wchnschr. **59**:121, 1929.

In confirmation of the work of Schütz and Wöhlisch, Hallauer found it possible to remove the specific agglutinogens from human erythrocytes by repeated washing with isotonic salt solution. Group B agglutinogen was more readily removed than that of group A. In the case of group AB erythrocytes, the B agglutinogen could be completely washed out, the remaining A component causing the corpuscles to react like those of group A. Working more particularly with groups A and B, Hallauer found that the washings of group A erythrocytes caused a flocculent precipitate in the presence of group B serum; Group B corpuscle washings yielded a similar precipitate with group A serum. When rabbits were immunized with the washings of group A or group B erythrocytes, there was obtained an antiserum which agglutinated specifically its homologous corpuscles and had only slight activity for erythrocytes of heterologous groups. With such antiserums it was possible to cause passive sensitization of guinea-pigs, death from anaphylactic shock resulting when the homologous erythrocytes were later injected. That death was not due to intracapillary agglutination was proved by the fact that no ill effects occurred if antiserum and corpuscles were injected within fifteen minutes of each other; a latent period between antiserum and corpuscle injection was necessary if death occurred, such a latent period being the criterion of the passive anaphylaxis experiment.

O. T. SCHULTZ.

ISO-ANTIBODIES IN MOTHER AND FETUS. NILE LIEDBERG, Acta path. et microbiol. Scandinav. **6**:1, 1929.

The blood groups of 200 mothers and their 200 new-born infants were determined. In 116 children the groups were the same as in the mothers; in all children the receptor was qualitatively determined at birth, while the iso-agglutinin was present in only 60. In seven children agglutinins were present which differed from those of the mothers and indicated that a child may develop its own agglutinin during fetal life. Normal hemolysin for sheep corpuscles was transmitted from mother to fetus in only a few instances and whether the group of the child is the same or differs from that of the mother seemed to make no difference. Isohemolysin occurs in the blood of some new-born infants, and the resulting hindrance to agglutination may be avoided by inactivation of the serum which may even increase the agglutinative titer. Intoxications of pregnancy, birth difficulties or icterus neonatorum do not seem to be related to blood grouping.

FROM AUTHOR'S SUMMARY.

ISOHEMAGGLUTINATION IN MOTHERS AND NEW-BORN CHILDREN. P. MORVILLE, Acta path. et microbiol. Scandinav. **6**:39, 1929.

The isohemagglutinative groups were determined for 500 mothers and their 518 children, of whom 63.1 per cent belong to the same blood group as the mother,

and 61.2 per cent had iso-agglutinin present at birth. When mother and child belonged to the same group iso-agglutinin was more frequently found at birth, in 95 per cent when the group was O as contrasted with about 50 per cent when the group was A or B. When the group of the child differed from that of the mother iso-agglutinin was present in the child at birth only when one of them was in group O, and a child in group O with a mother in group A or B does not have the agglutinin combination a + b, but has only the agglutinin which is present in the mother. The conclusions from these studies of children at birth and at different ages are that iso-agglutinin passes from the mother's blood to the fetal blood in every instance but is often removed by the child's corpuscles, that the agglutinin present at birth is not the child's own, that the child's own agglutinin is in most cases developed at the end of four months but cannot always be expected in less than one year, and that the receptor (agglutinogen) is always present at birth though possibly weak and not easily determined. Certain paradoxic cases are described. Agglutinin and receptor are regarded as related properties due not to different, mutually independent heredity-factors, but to various hereditarily regulated stages of the same factor, and on the basis of this theory the group characteristics become an expression of genuine immunization. Experimental support is considered essential.

ETHEL B. PERRY.

Tumors

LYMPHO-EPITHELIOMA. JAMES EWING, Am. J. Path. **5**:99, 1929.

The present available data seem to call for the recognition of a particular form of epidermoid carcinoma occurring especially in the nasopharynx and designated by Regaud and Schmincke as lympho-epithelioma. The tumors arise from modified epithelium overlying lymphoid structures in the tonsils, the base of the tongue and the nasopharynx. They occur at all ages, frequently in young subjects, grow slowly, are often overlooked, tend to produce early metastases in the neck and later widespread extensions to the liver and bone marrow, and are generally fatal. They exhibit a marked primary response to radiation. The diagnosis must be based on the structure, which shows sheets of pale staining epithelial cells, often in syncytia, and infiltrated with many lymphocytes, both in the primary tumor and in metastases. The diagnosis may not be based on clinical appearances, course, location or radiosensitivity. Other tumors of the same regions are radiosensitive and produce early metastases to lymph nodes, bones and viscera. Anaplastic carcinomas may be distinguished by their more rapid course and cellular structure. The exact scope of lympho-epithelioma is not yet clear. Tumors of transitional epithelium located in many areas of the nasopharynx and lining the ducts of mucous glands seem to produce tumors showing many of the characteristics of lympho-epithelioma. It seems possible that the admixture of lymphocytes may be the result of a low grade inflammatory process occurring in certain other tumors, but their appearance in metastases is probably not to be explained in this way.

AUTHOR'S SUMMARY.

BIOPSY HISTOLOGY IN THE GRADING OF RECTAL CARCINOMA. FRED W. STEWART and JOHN W. SPIES, Am. J. Path. **5**:109, 1929.

The histologic grading of rectal carcinomas in accordance with the suggestions of Rankin and Broders is of value in estimating the probable course of the disease. Small biopsy specimens are sufficient for such grading. Repeated biopsies do not show that change in type occurs sufficiently often during the course of the disease to interfere seriously with the prognosis suggested by the grade given at the time of the first biopsy.

AUTHORS' SUMMARY.

NEURO-EPITHELIOMA OF THE CEREBELLUM. PAUL C. BUCY and WENDELL S. MUNCIE, Am. J. Path. **5**:157, 1929.

Neuro-epitheliomas are composed of primitive spongioblasts, and, as such, arise from the parent cells of ependymal tissue. Though more commonly arising from the ependyma of the spinal cord and from the retina, they may arise from ependyma elsewhere. A review of the literature shows that the case here reported is the fifth authentic case of neuro-epithelioma of the brain, and the second involving the cerebellum.

AUTHORS' SUMMARY.

SO-CALLED INFECTIOUS SARCOMA OF THE DOG IN AN UNUSUAL ANATOMIC SITUATION. WILLIAM H. FELDMAN, Am. J. Path. **5**:183, 1929.

The more important literature pertaining to the transmissible lymphosarcoma of dogs is reviewed. A case is described in which two tumors, which morphologically were indistinguishable from transmissible sarcoma of the genitals, appeared respectively in the orbital space and under the skin of the frontal region of a young dog. The genitals were not affected. Although transplantation was not attempted, there seems sufficient histologic evidence to substantiate a diagnosis of transmissible lymphosarcoma. The word "transmissible" is preferable to the older term "infectious," since there is not evidence bacteriologically or otherwise that these growths are dependent for their origin on an infective factor in the accepted sense of the word. It could not be determined whether each growth had a spontaneous origin or whether one represented a metastasis from the other. The possibility of the tumors being the result of transplantations from a vaginal tumor of the mother at the time of birth was considered, but this was not subject to proof since the parentage of the puppy could not be traced.

AUTHOR'S SUMMARY.

THE REACTION OF THE SKIN TO OILS AND TARS. C. C. TWORT and J. M. TWORT, J. Hyg. **28**:219, 1928.

A number of substances applied to the skin may cause a hyperplasia, which may recede when the irritant is removed or become the site of a malignant tumor. Acute hyperplasia is more liable to recede than chronic. Agents that produce acute hyperplasia differ in their ability to excite the formation of tumor. Agents can be concentrated so that weak tumor producers may become strong ones, these tumors rarely becoming malignant. The malignant possibilities of agents vary although all other qualities may be equal. The epithelial cells acquire a certain degree of tolerance for agents applied. They can be rendered hypersensitive to tar applications, however, by treating them originally with other agents.

H. E. LANDT.

TUMOR IMMUNITY. THOMAS LUMSDEN, J. Path. & Bact. **32**:185, 1929.

The existence in the fresh serum of normal animals of nonspecific cytotoxins (heterotoxins) effective against the tumor and normal tissue cells of foreign animals is demonstrated. These cytotoxins are of the nature of labile immune bodies. They are ineffective in the absence of complement. The tumor and normal tissue cells of any particular species are specifically "protected" against damage by homologous cytotoxins, whether naturally existing or experimentally produced. The nature of this "protection" has been investigated and is described.

AUTHOR'S SUMMARY.

IMMUNE REACTIONS AND CANCER. F. C. PYBUS and H. R. WHITEHEAD, J. Path. & Bact. **32**:195, 1929.

The serum of rabbits immunized against mouse carcinoma has a harmful effect on mouse carcinoma, heart and kidney cells growing in vitro. The effect on heart cells is slightly less pronounced than on carcinoma and kidney cells, but there is no marked specificity of the immune serum for carcinoma cells. The

serum of a rabbit immunized against human carcinoma still serves as a culture medium for mouse carcinoma, although it is not so good as normal rabbit serum. The growth of normal mouse tissues is also not so good in the immune serum. These experiments contribute no evidence, therefore, to prove the existence of antibodies common to the malignant cells of different animal species.

AUTHORS' SUMMARY.

EXPERIMENTAL CANCER AND HALOGEN SALTS OF MAGNESIUM. PIERRE DELBET, HENRI GODARD and C. PALIOS, Bull. de l'Ass. franç. p. l'étude du cancer **27**:515, 1928.

The experiments of Delbet and his associates were performed on guinea-pigs in whose gallbladder they inserted sterile gravel. The animals were divided into two groups one of which was treated with salts of magnesium and the other served as controls. The guinea-pigs were killed 24, 63, 72, 90 and 105 days after the operation. Those animals that have not received the salts developed marked cholecystitis with vesicular lesion which suggested a malignant disease. The animals treated with salts of magnesium showed no disease of the gallbladder.

B. M. FRIED.

THE ACTION OF HALOGEN SALTS OF MAGNESIUM ON THE EVOLUTION OF GRAFTED CANCER. PIERRE DELBET and C. PALIOSE, Bull. de l'Ass. franç. p. l'étude du cancer **27**:525, 1928.

In a previous note Delbet reported experiments on white mice to the effect that the growth of an epithelioma is considerably retarded when the rodent is treated with salts of magnesium and also that it is impossible to reinoculate a tumor which has grown in mice treated with this salt.

These experiments concern themselves with the effect of the salts of magnesium of the growth of a sarcoma and of three different types of epitheliomas. The "magnesiated" animals received bread soaked in the salt of magnesium and also subcutaneous injections of the salt which was composed of magnesium chlorate, magnesium bromide, magnesium iodide, 0.0002 Gm., and magnesium fluoride. The experiments have shown that the tumor progressed much slower in animals that received the drug than in the controls.

B. M. FRIED.

THE TREATMENT OF CANCER WITH COLLOIDAL LEAD. G. LOEWY and J. LOISELEUR, Bull. de l'Ass. franç. p. l'études du cancer **27**:549, 1928.

Borrel has produced evidences to show that glycogen has a particular affinity for the cancerous cells. Loewy and Loiseleur have succeeded in fixing colloidal lead on glycogen which they thought might serve as a vehicle to transport the metal toward the malignant cell. It is remarkable that the chemical thus prepared is supported in much higher doses than when administered without glycogen. It leads, however, to an anemia characterized by the usual signs and symptoms of plumbism. The glycogen-lead treatment was applied to different types of tumors (carcinoma of breast, osteogenetic sarcoma, melanotic sarcoma) without any appreciable results.

B. M. FRIED.

EMBRYONAL GRAFTS AND MALIGNANT TUMORS. N. PETROFF and N. KROTKINA, Bull. de l'Ass. franç. p. l'étude du cancer **27**:566, 1928.

The authors have performed experiments on white rats by injecting into these rodents embryonic pulp from rats varying from 1 to 3 cm. in length. This was combined with: (1) indol and injected into the peritoneum; (2) lactic acid and injected subcutaneously into the gluteal region; (3) arsenic and injected subcutaneously into the thigh.

The first series led to the development of insignificant wounds. In the second series they noted the appearance of firm nodules having a tendency toward absorption. Finally, of twenty-six rats of the third series, two animals developed malignant growths identified as sarcomas.

The article represents a review of previous works on the same subject and also a discussion on the mechanism of the "malignisation" of the animal injected with the embryonic pulp. The authors believe that in instances when the malignant disease follows immediately the injection of pulp it is due to transformation of the injected material into a malignant disease; in those cases when a disease occurs months after inoculation it is caused by the hosts' cells under the influence of the embryonic pulp.

B. M. FRIED.

THE RELATIONSHIP BETWEEN THE PERIPHERAL NERVES AND THE DEVELOPMENT OF CANCER. ITCHIKAWA (KOITCHI), Bull. de l'Ass. franç. p. l'étude du cancer **27**:590, 1928.

Itchikawa states that a proliferation of nerve fibers occurs in benign or malignant tumors whether spontaneous or experimental. He also noted that the pre-existing nerve fibers degenerate in neoplastic tissues. He thinks that the rôle of the nerves is most important in the development as well as in the regression of tumors.

B. M. FRIED.

LESIONS IN THE RABBIT'S EAR FROM PAINTING AND FRICTION WITH TAR. A. BABES and SERBANESCO, Bull. de l'Ass. franç. p. l'étude du cancer **27**:597, 1928.

The difference between the two procedures as seen in the early stages is as follows: When the tar is applied to the ear by friction, it induces a lesion akin to a senile keratosis which is regarded as a precancerous stage. Simple painting of the rabbit's ear with tar causes in the beginning a mere dyskeratosis (maladie de Darier) which as far as is known has nothing to do with a malignant disease. The authors maintain that the different results obtained are purely mechanical in origin.

B. M. FRIED.

THE APPEARANCE OF A CANCER THE THIRTEENTH DAY AFTER THE ONSET OF PAINTING WITH TAR. A. BABES, Bull. de l'Ass. franç. p. l'étude du cancer **27**:605, 1928.

In a few experiments with painting a rabbit's ear with tar, Babes obtained the appearance of an epithelioma within about two weeks after the first application of the irritant. In his opinion two factors are required for the appearance of tar cancer: (1) a chemical, and (2) a mechanical. The host himself, that is, the ear of the rabbit, and also the quality of the tar in all probability play a rôle in the precocious appearance of the malignant disease.

B. M. FRIED.

THE STRUCTURE OF THE CELLS IN UTERINE CARCINOMA. LAIMI LEIDENIUS, Arb. a. d. path. Inst. du Helsingfors. **5**:334, 1928.

This is an elaborate and thorough study of a large material the details of which are best studied in the original article. In all forms of uterine carcinoma, including cervical carcinoma treated with radium, the various structures of the cytoplasm of the normal epithelial cells are recognizable in the carcinoma cell; frequently, however, the characteristics are changed in some way or other.

CARCINOMA OF THECA INTERNA OF LUTEIN CYST. J. WALLART, Arch. f. Gynäk. **135**:485, 1929.

The growth occurred in a woman, aged 45, three years after giving birth to a healthy child.

Technical

THE VALUE OF THE COSTA REACTION FOR THE DEMONSTRATION OF ACTIVE TUBERCULOSIS. M. TROJAN and F. PONGOR, Ztschr. f. Tuberk. **52**:209, 1928.

The mechanism of the reaction is still unknown. It is considered to be of definite value for the diagnosis of activity in tuberculosis. Although the reaction is nonspecific, it is independent of menstruation. The technic is simple and quick, and requires only three drops of blood. It is therefore of wide applicability even in private practice.

MAX PINNER.

DEMONSTRATION OF TUBERCLE BACILLI IN THE SPUTUM WITH THE DARK FIELD METHOD. S. VON STUBENRAUCH, Ztschr. f. Tuberk. **53**:122, 1929.

The demonstration of tubercle bacilli with the dark field method is easy, but no more specimens are found positive than with the usual methods.

MAX PINNER.

THE COSTA REACTION IN TUBERCULOSIS IN CHILDHOOD. K. NÜSSEL and H. HELBACH, Ztschr. f. Tuberk. **52**:301, 1928.

The reaction is less sensitive than the sedimentation reaction of erythrocytes, but it is recommended particularly for examination of children because it requires only a small amount of blood.

MAX PINNER.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, April 8, 1929

ESMOND R. LONG, *President, in the Chair*

SPONTANEOUS CHRONIC GLOMERULONEPHRITIS IN A RAT. R. H. JAFFÉ.

The numerous fruitless attempts to produce experimentally a condition similar to the glomerulonephritis in man and the rareness of the spontaneous occurrence of such a condition in animals warrant the demonstration of the renal changes that were observed in an apparently normal rat. The rat was one of the controls used by Prof. W. C. Rose of the chemistry department of the University of Illinois in his studies on the effect of certain diets on the kidneys. It was under observation for two hundred and ninety-seven days and had received fully adequate food, permitting rapid growth. At the end of the experiment, the animal was killed, and since it was considered normal the urine was not examined. Except concerning the kidneys, autopsy did not yield any unusual observations. The weight of each kidney was 1.2 Gm. The weight of the heart was not taken. Examination of the blood revealed a marked increase of the nonprotein nitrogen, which was 101.4 mg. per hundred cubic centimeters as compared to 45 mg. for the normal rat.

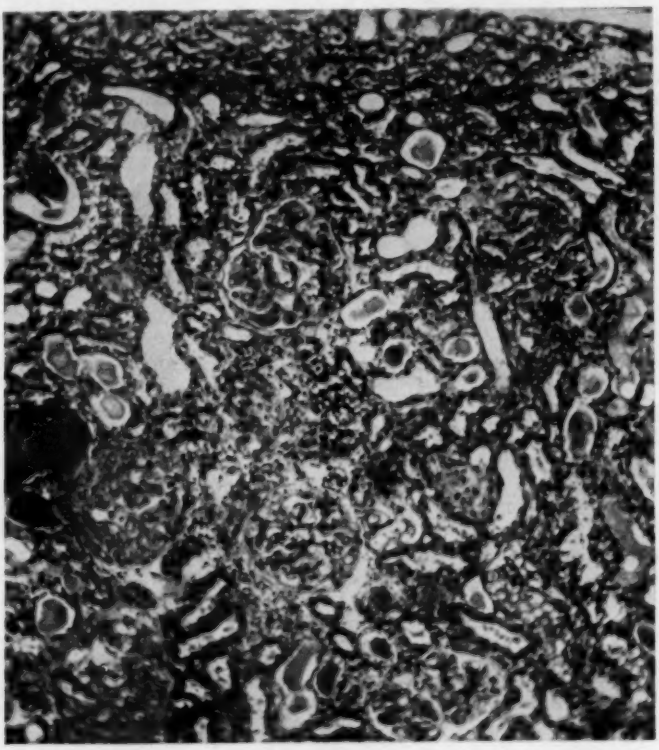
The kidneys, which were mailed to me fixed with formaldehyde, were a light yellow-gray. The surface to which the capsule was adherent showed flat granular elevations just visible to the naked eye and separated by shallow depressions of a darker gray. On sections made by cutting, there was no difference in color between the cortex and the medulla, both being of the same pale yellowish-gray hue.

Under the microscope, there was great similarity to the histologic changes of chronic glomerulonephritis in man. This similarity involved the changes of the glomeruli and tubuli as well as those of the stroma and the blood vessels. In the glomeruli, various stages of hyaline obliteration were observed. There were large glomeruli with distended tufts which were filled with swollen and proliferated endothelial cells. The cytoplasm of these cells was filled with fat droplets. The epithelium of Bowman's capsule too, was found proliferated and, in places, was arranged in several layers. The capsular space was reduced to a narrow slit or had entirely disappeared. Other glomeruli showed a diffuse hyaline degeneration of the wall of the tufts, the tips of which fused with the thickened capsule. Single lipoid-filled cells were embedded with the hyaline material. Finally, there were glomeruli completely transformed into a hyaline body.

Many of the convoluted tubuli were atrophic. The small epithelial cells were filled with single and double refractive fat droplets. The atrophic areas alternated with others in which the tubuli were wide and were lined by a flat epithelium. Their lumen contained a pale-stained homogeneous material. Here and there was a small cyst with a basophilic colloid-like content. The collecting tubuli of the medulla were dilated and filled with hyaline casts, which, in the sections stained with sudan III, took a pale yellowish-gray.

The stroma was increased especially about the atrophic tubuli. There were small perivascular accumulations of lymphocytes. The small arteries, in particular the interlobular branches stood out distinctly because of the thickness of the wall. The muscle fibers of the media were hypertrophic, and there was a thin layer of hyaline material between the endothelium and the internal elastic membrane. In places the entire wall was transformed into a hyaline material. In these places, fat stains revealed lipoid deposits.

In its details as well as in the combination of these details the kidney of this rat was an exact duplicate of a human secondary contracted kidney. There was the hyaline obliteration of the glomeruli on an inflammatory basis, the complicating lipoid nephrosis and the arteriosclerosis. The change was entirely different from what frequently is described as an experimental nephritis and which is but the result of a severe degenerative process of the tubular epithelium, a chronic nephrosis. It is also different from the spontaneous renal lesions often encountered, especially in dogs and rabbits, which are interstitial inflammatory processes from ascending urinary infections or from metastatic embolic processes.



Spontaneous chronic glomerulonephritis in a rat. Note the various stages of hyaline obliteration of the glomeruli, the atrophic and distended tubuli contorti and the hyaline casts in the latter. There are two small cysts near the left edge. Stained with hematoxylin and eosin; × 100.

DISCUSSION

H. G. WELLS: A number of the mice in Miss Slye's collection had glomerulonephritis associated with an enlarged heart and hydrothorax. Crescent-shaped hyperplasias of the cells lining Bowman's capsule were never observed.

THORACIC NEUROBLASTOMA. GEORGE RUKSTINAT and H. D. COUNTRYMAN.

A colored girl, aged 3 years, became unable to walk following intermittent attacks of "cold and fever" for four months. She had characteristic evidences of consolidation in the right lung and in addition accentuated right patellar and achilles

reflexes, right patellar and ankle clonus and a bilateral Babinski sign. X-ray plates disclosed a neoplasm in the right lung field extending across the midline downward to the level of the eighth rib peripherally and medially to the cardiodiaphragmatic angle. The essential items of the anatomic diagnosis were: primary mediastinal neurocytoma with hemorrhage; tumor erosion of the second and third thoracic vertebrae, and marked compression atelectasis of the right lung. The tumor, 13 by 10 by 6 cm., was attached to the apex of the right lung and right side of the mediastinum. Its rough fibrous capsule was from 1 to 2 mm. thick, dull gray and speckled occasionally with pin-point yellow dots of fat. The surface of the tumor, particularly posteriorly, was irregular from nodules from 1.5 to 4 cm. in diameter; about half of these were soft, the rest firm. On broad surfaces made by cutting, the upper one third of the mass consisted of firm grayish-pink tissue dotted irregularly, about 5 per cent by pin-point yellow specks. In some places this gray tissue was arranged in longitudinal and interlacing fine bundles; in others it formed compartments from 2 to 10 mm. in diameter, filled with friable yellow masses. The arrangement resembled most a sponge into the pores of which sawdust had been packed. Sections of the tumor were stained with hematoxylin and eosin, phosphotungstic acid hematoxylin, sudan III and by the special methods of Weigert-Pal and Bielschowsky. The tumor capsule was heavily cellular with fibroblasts and, generally slightly infiltrated with small lymphocytes. Where it bordered on the spongy portions of the tumor it was invaded in irregular serrations by clumps of small round to oval cells only slightly larger than a small lymphocyte with a hyperchromatic nucleus and a peripheral rim of cytoplasm only about one-fifteenth the diameter of the nucleus. Occasionally, these cells were in cords from five to six cells wide, but more often they appeared in medullary masses. Occasionally, there were annular arrangements of these cells and from seven to twelve encircled a finely speckled mass. These were regarded as rosets. More centrally in the tumor the small cells gave way to a delicately fibrillar structure enclosing purple hyperchromatic masses in places of which were hints of necrotic cell bodies. These masses represented the yellow flecks noted grossly. With Weigert-Pal stains huge tangles of neurofibrils appeared between the small type of cells and definite processes were discernible on large ganglion cells which occurred in definite clumps near the softer parts of the tumor. Masses of neuroblasts were evident in the peribronchial lymphatics. The tumor herein reported was believed to be uncommon and represented a combination of a ganglioneuroma and a neuroblastoma.

DISCUSSION

PERCIVAL BAILEY: Three distinct types of sympathetic tumors may be distinguished, usually called chromaffin tumors, ganglioneuroma and neuroblastoma. I object to the last term. The implication is that the neoplastic cells are neuroblasts. This implication is based largely on negative evidence; the fibrillary material does not stain with aniline-blue nor with phosphotungstic acid hematoxylin; being neither collagen nor neuroglia it must be nervous fibers. The conclusion does not follow even though aniline-blue stained all the mesodermal fibrillae and hematoxylin all the neuroglia. The only positive evidence is based on the results of Bielschowsky's method, which is notoriously unspecific. Herxheimer's illustrations show fibrils which are much more characteristic of reticulin than of nervous fibers. The structure of the more differentiated tumors, the ganglioneuromas, shows that the neoplastic cells are multipotential and may form nervous cells, neurinomatous cells or chromaffin cells. It seems better to employ a noncomittal term such as sympathicoblastoma for the undifferentiated tumors.

H. G. WELLS: I have recently seen a mediastinal tumor in a child, producing pressure on the right side of the trachea. Histologically, it is a ganglion cell tumor.

HEMANGIOMA OF BONE. PAUL C. BUCY.

A pathologic study of seven cases of hemangioma of the bone and a review of the literature were presented. Hemangioma of the bone is a rare clinical

entity; only thirty-nine clinical cases are known. Of these, thirteen were located in the skull, twelve in the vertebrae and the remaining fourteen in various other bones of the body. Pathologically, hemangioma of the vertebrae is common, having been demonstrated by Töpfer in more than 11 per cent of all bodies examined. However, these growths rarely produce symptoms. Hemangioma of the bone is more prevalent in females than in males at a ratio of about 55 : 45, and is more commonly found during the fourth and fifth decades. Multiple lesions involving other bones or soft tissues are frequent.

The material presented confirmed Hitzrot's statement that hemangiomas of the long bones occur near the epiphyseal line. Grossly, the lesions presented a swelling of the involved bone covered by intact periosteum. The tumors were of bony hardness and on section were seen to be traversed by numerous bony trabeculae between which the vascular tissue could be seen. Cystic forms have been reported. Microscopically, the series included six cavernous hemangiomas and a capillary hemangioma of the ulna. The difference was only one of size of the vascular channels. In the cavernous hemangiomas the channels were very large, while the spaces in the capillary hemangiomas were but little larger than capillaries. Practically no endothelial proliferation was seen. The amount of intervascular connective tissue varied greatly in different cases.

Study of the spicules of bone revealed two types of changes, formative and destructive. The former were characterized by the formation of new bone by osteoblasts which could be seen as a single layer of cells along the spicules of bone, and by the ossification of fibrocartilage which was particularly interesting on the surface of the laminae in the case of hemangioma of the vertebrae. Destructive changes were seen in the numerous necrotic pieces of bone present and in the erosion of the bone by numerous multinucleated giant cell osteoclasts.

Several lantern slides illustrating the various histologic characteristics were shown.

The complete report is published in Am. J. Path. **5**:381 (July) 1929.

CELLULAR CHANGES OF THE ARACHNOID IN LEPTOMENINGITIS. THEODORE T. STONE.

Eleven cases of leptomeningitis were studied: three meningococcic, six tuberculous and two syphilitic. In the epidemic meningococcic and purulent types, study of the arachnoid revealed the presence of large, circular or oval cells which appeared attached to the inner surface of the arachnoid membrane. These cells contained an eccentrically placed nucleus with cytoplasm-containing substances that stained black with osmic acid and in many instances contained structures resembling cocci. In other parts of sections in these types evidence of arachnoid cluster formation could be made out. Many parts of the arachnoid were devoid of cells. In the latter instances, the subarachnoid space contained large cells with eccentric nuclei and reticulated cytoplasm. The latter was made up of inert bodies, fat globules, organisms and blood cells.

In tuberculous and syphilitic leptomeningitis no such relationship existed between the arachnoid membrane and the subarachnoid space. In early acute cases of leptomeningitis in man, the cells lining the arachnoid and trabeculae may become macrophages.

RETROPERITONEAL CYSTS. W. H. DROEGEMUELLER, JR.

The first reported case of a retroperitoneal cyst was probably that described by the Florentine anatomist, Benivieni, in 1507 (De abditis nonnullis ac merandis moborum, et sanationum cousis, Florence, 1507). The first comprehensive résumé of the subject was published by Hahn in 1887 (Berl. klin. Wchnschr., 1887, p. 408). Five years later Braquehaye (Arch. gén. de méd., 1892, vol 2) divided the history of retroperitoneal cysts into three periods: (1) the "anatomical period" from the time of Benivieni to 1850; (2) the period of "surgical interference on mistaken diagnosis" from 1850 to 1880, and (3) the "clinical surgical period" after 1880. In 1900, Dowd (Ann. Surg. **32**:515, 1900) pointed out the embryonal origin of

many of these cysts. In 1907, just four hundred years after Benivieni's report, Niosi (Virchows Arch. f. path. Anat. **190**:217, 1907) collected 184 cases from the literature and classified them into: (1) cysts of intestinal origin; (2) mesenteric dermoid cysts; (3) cysts derived from the remains of the urogenital tract, and (4) a miscellaneous group of these cysts that did not belong to the three types differentiated by him.

The most satisfactory classification of retroperitoneal cysts thus far presented is that of R. M. Handfield-Jones (Brit. J. Surg. **12**:119, 1924), which is as follows: cysts arising from cell inclusions such as dermoid cysts; parasitic cysts; traumatic blood cysts; cysts developing in fully formed organs, as the retention cysts of the kidney and pancreas; lymphatic cysts, and cysts of urogenital origin.

To this list is added a further group differentiated by A. Stoney (Brit. J. Surg. **12**:789, 1925); namely, cysts associated with the mesocolon, which are apparently retroperitoneal in position.

Retroperitoneal parasitic, blood and dermoid cysts and cysts attached to adult organs, each have outstanding characteristics that make their classification certain. The differentiation of cysts of urogenital, lymphatic and mesocolic origin, however, is a much more difficult problem. for grossly, and in many respects microscopically, these cysts have essentially the same characteristics.

Lymphatic cysts are of comparatively small size and are of two types: chylous and serous. The former is recognized by the character of its contents and develops in the lymphatics which receive lymph from the intestines. The serous lymphatic cysts that are small are probably derived from simple dilatation of the lymphatics. It has been suggested that the larger cysts arise from anomalies in the primitive retroperitoneal lymph sac.

The pronephros, mesonephros and metanephros form the embryonic urogenital system, which undergoes a series of complex changes in growth and regression in the retroperitoneal tissues. In the development of the urogenital system there is opportunity for delay or failure in the normal degeneration of some tubular structure which may thus be a source of cyst formation. The tubules of the mesonephros have been observed long after they normally degenerate. These urogenital cysts have a dense fibrous wall, are usually monolocular, contain a clear serous fluid and are lined with a low columnar epithelium.

Mesocolic cysts may develop either in the mesocolon or between the mesocolon and the posterior celomic wall.

Following the elongation and contra-clockwise rotation of the developing gastrointestinal tract in early fetal life, the peritoneum covering the posterior abdominal wall and the mesocolon normally blend. When fusion is imperfect the large intestine becomes provided with a mesentery; when fusion occurs at the periphery but not over the whole surface, small spaces are left in which fluid may accumulate to form cysts. Such a cyst would be situated anterior to the retroperitoneal structures and have a lining of mesothelium.

The other type of cyst that develops within the mesocolon, according to the classification of some authors is a true mesenteric cyst, that is, one definitely located within the mesentery. These cysts arise from embryonic intestinal diverticula that have been observed in the development of the embryo. Their walls are lined with a columnar epithelium similar to that lining the intestine and are composed of fibrous tissue and smooth muscle.

The case here reported is that of a man, aged 70, who entered the Alexian Brothers Hospital on Feb. 17, 1929. The patient was in a stuporous condition and a satisfactory history was not obtainable. When awake he held his hand on the left side of his abdomen, suggesting some discomfort in that region. The patient's daughter said that for many years he had had a palpable mass in the lower part of the left side of the abdomen. This mass is said to have increased markedly in size during the last forty-eight hours of life. Cystoscopic examination revealed a normal bladder. The patient died on Feb. 20, 1929.

The postmortem examination by Dr. J. P. Simonds revealed the following conditions: arteriosclerosis of the coronary arteries with calcification; chronic myocardial fibrosis; brown atrophy of the heart; atheromatous changes in the mitral and aortic valves; hydropericardium; atheroma of the aorta; primary carcinoma of the bronchus to the left upper lobe with invasion and occlusion of the pulmonary artery to that lobe; gangrene of the upper lobe and of the upper part of the lower lobe of the left lung; healed, calcified tuberculosis of the right lung; chronic fibrous pleurisy, obliterative on the left side; chronic perihepatitis; perisplenitis cartilaginea; chronic pancreatitis; arteriosclerotic contractions of the kidneys; multiple retention cysts of the right kidney, and large left retroperitoneal cyst.

This cyst was in the left side of the abdominal cavity, was ovoid, contained 2 liters of clear yellowish fluid and measured 30 cm. in length by 22 cm. in diameter. The transverse colon passed along its upper surface, and the splenic flexure lay behind its upper end. The descending colon, which was empty, passed downward along the lateral surface for about three fourths of the length of the cyst, then passed over the cyst to the right, thence down and back to a position immediately beneath the inferior surface of the cyst. The root of the mesentery and the duodenum was pushed to the right; the spleen lay behind and to the left, and the stomach rested on the upper surface of the cyst. The left kidney lay well above and slightly behind the cyst and the left ureter passed down the posterior and lateral surface of the cyst to which it was adherent. The aorta was also adherent to it and pushed to the right.

Five centimeters from the upper end of the cyst was a constriction. Above this constriction the cyst bulged slightly and then tapered to a thin-walled tube, 6 cm. in length, which turned downward under the main cyst. This tubular prolongation varied between from 3 to 10 mm. in diameter, and lay along the left half of the front of the second and third lumbar vertebrae. Extending from the apex of the cyst downward along the posterior surface of the large cyst was a firm yellowish-red translucent and tortuous cordlike structure from about 1 to 2 mm. in diameter, resembling a dilated lymphatic, and ended below in a somewhat purplish trilobed mass, each lobe measuring approximately 7 mm. in diameter and 5 mm. in thickness. When this cordlike structure and the trilobed mass were incised after fixation in formaldehyde, they were found to be filled with a firmly coagulated translucent orange colored material.

The lining of the tubular prolongation of the main cyst was smooth and consisted of an incomplete single layer of flat cells; that of the cyst itself was roughened by calcified masses and no definite layer of lining cells was found. Microscopically, the wall of the cyst was composed of a dense fibrous tissue.

The specific gravity of the fluid was 1.024. It coagulated on standing and became dark brown. Examination of the sediment centrifugated from 50 cc. of the fluid showed a few red blood corpuscles and leukocytes.

The cyst was probably of embryonic origin. Its general relations did not seem to correspond with the urogenital type. If the cyst arose from a mesonephric tubule, one would expect it to lie posterior to the ureter and to be lined with cuboidal epithelium. That this cyst belonged to the lymphatic type cannot be definitely excluded. If it arose from the portion of the retroperitoneal lymph sac which is median in position, one would not expect to find the relations of the cyst as they were; the ureter would be anterior to the cyst.

The structure, and especially the relations of this cyst, did correspond with the mesocolic type. From its position, lying at first medial and then posterior to the descending colon, inferior to the transverse colon, superior to the sigmoid and anterior to the ureter, it seemed reasonable to assume that this cyst developed in a sac formed by the incomplete fusion of the mesocolon and the posterior abdominal wall. Hence, I found a thick fibrous wall and a lining of mesothelium which had been partly destroyed by the marked calcification of its inner surface.

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, April 11, 1929

HARRISON S. MARTLAND, M.D., *in the Chair*

THE SIGNIFICANCE OF HISTOLOGIC EXAMINATION OF THE SKIN IN CLINICAL DIAGNOSIS. WALTER J. HIGHMAN.

General pathologists can scarcely realize how much has been written on pathologic conditions of the skin. There have been about twenty outstanding skin pathologists throughout the world, with perhaps an equal number now coming forward, but a bulky literature attests the fact that more has been written on the subject than the few competent authors could possibly have produced. In almost every dermatologic publication an undue amount of space is devoted to histologic description, and if these descriptions were shuffled and redistributed at random no one would be the wiser, for most of them are vague and unconvincing. With little talent for portrayal, unshaded references to round cells, plasma cells, perivascular infiltration and other stock phrases are employed, with the net result of nothing distinctive in the description.

The habit has been formed of calling such a description a histologic diagnosis, and the clinician entertains a feeling of outrage if microscopic study does not furnish him the desired diagnosis, or if the observations are not in accord with his hopes. To appreciate the situation, a nondermatologist must be reminded that there are more than 500 so-called skin diseases of which the inflammations are usually not distinctive as to microscopic appearance. This fact is the essential one to be considered.

For a moment, however, a short digression will narrow the issue. Tumors of the skin are distinctive enough histologically. In fact, the clinical identification of neoplasms falls so far short of the microscopic identification that the latter becomes an imperative aid in the diagnosis of tumor and in the recognition of the subtler types of nevi, or better, embryonal anomalies. All the connective tissue and most of the epithelial neoplasms, both benign and malignant, including such lesions as molluscum contagiosum, pointed condylomas and the like, possess characteristic minute structure. The majority of regressive changes, including dystrophies, like the sclerodermas, atrophies, colloid alteration and calcification of the skin, are individual under the microscope as are also many of the infections, provided the specific parasite can be demonstrated; however, on mere anatomic grounds, this is by no means so. But in noninfectious inflammations of the skin and in some other types of lesions, fundamental difficulties requiring explanation arise, which render the microscope scarcely serviceable in diagnosis.

Inflammatory dermatoses are numerous, and dermatologists have differentiated them from one another with astute overrefinement, their concepts having been descriptively formed with scant reference to etiology. What little is known of the causes of skin diseases indicates strikingly that eruptions due to a single agent may vary widely in appearance and, conversely, that unrelated agents may produce identical dermatoses. An example of the first would be the various iodide lesions; of the second, the toxic erythema or the wheal. Thus, the very foundation of descriptive dermatology is faulty. Moreover, these facts are reflected in the histology of inflammations of the skin. The elements composing microscopic architecture are few, and the range of their combinations is not wide. But the principles governing macroscopic pathology of the skin, which is what clinical dermatology is, have also governed its microscopic pathology, and keen attention has been given to the most trifling minute changes, in the hope that clinical limitations would be thus supplemented. In the main the effort has been a failure, and as far as inflammatory dermatoses are concerned, it seems that microscopic pathology offers little aid in diagnosis. Moreover, to talk of histologic diagnosis in this connection is unphilosophic.

A few inflammations have an almost uniformly characteristic aspect, if not a pathognomonic one. When mast cells are abundant, lichen planus and urticaria pigmentosa are such. Psoriasis, parapsoriasis, lupus erythematosus, eczema and some forms of lichenification are often distinctive enough to be recognized for what they are, under the microscope. Their identification, however, rests on such meticulous details that there is no opportunity in a paper of this sort to do more than state the fact. More often, an arbitrary construction of the slides is unjustified. The erythemas, urticaria, pemphigus and related diseases, the general scaling eruptions known as exfoliative dermatitides, ichthyosis, and another score or so of inflammations, subject to their stage, all present the appearance of acute, subacute or chronic exudative inflammation or productive inflammation, as the case may be, with certain more or less dominant features in the epidermis or cutis vera or individual elements of these which might correctly guide an experienced dermatopathologist to venture an opinion as to the clinical nature of the lesion, but certainly no diagnosis.

Cutaneous syphilis, lepra, rhinoscleroma and tuberculosis in its multifarious aspects are often distinguishable from one another and from similar lesions caused by various fungi. But the most seasoned microscopist would not have the hardihood to be arbitrary in borderline cases. In lepra the lepra cells and in rhinoscleroma the rhinoscleroma cells and Russell bodies may furnish a clue, but not invariably. Other features would provide further tentative guides. Here, again, circumspection would necessarily be desirable, except when the parasite can be found; but this is scarcely a fair criterion under the conditions discussed in this paper, for the parasite might more easily be demonstrated outside the section.

The so-called lymphodermas, that is, infiltrations of the skin in leukemia, Hodgkin's disease and mycosis fungoides, are often typical enough to be identified by a shrewd observer. More frequently, though, this is not so; nor can the prodromal phases of these conditions be recognized with any certainty. Of the eruptive fevers, measles, scarlatina and the related erythemas are not distinctive; smallpox and chickenpox, and in this connection zoster are, within limits, distinctive. Certainly, however, to characterize this as diagnosis would be an exaggeration.

Thus histologic study of the skin is a first-rate diagnostic aid only for neoplasms. It is a fair diagnostic guide in granulomatous infections and in lymphatic infiltrations. In some of the dystrophies, it can also be so regarded. In inflammations only the microscopic appearance of lichen planus and urticaria pigmentosa is distinctive, but these conditions are clinically so obvious that their microscopic distinctiveness is of no practical importance. In all other inflammatory processes, although the microscopic structure is often suggestive, no justification exists for talking of such a thing as microscopic diagnosis. Therefore, cutaneous histologic study, aside from its bearing on neoplasms, is of no great value in clinical diagnosis.

But to drop the matter here is hardly fair, either. Pragmatic ends are not the only ones to be served in science. Two points must be discussed. First, clinical dermatology is enhanced by a grasp of the minute architecture of lesions of the skin, if not from the diagnostic, at least from the intellectual, side. Since the histology of lesions of the skin has been so emphasized in the literature, a clinician not conversant with its broader meaning, at least to the extent of understanding what a histologic description purports to convey, is handicapped, partly through illiteracy and partly because he may be misled by inadequately trained writers. Second, cutaneous microscopic changes constitute a highly specialized field with which the general pathologist is not necessarily conversant unless he has troubled himself to master its minutiae, in terms of clinical dermatology. He must be a reasonably good dermatologist to be a reasonably accurate interpreter of microscopic changes in lesions of the skin. Any general pathologist can easily so equip himself, but few do. Dermatology is, after all, not the black art. On the other hand, few dermatopathologists have concerned themselves sufficiently with general pathology. What is necessary is that the dermatologist, dermatopathologist and general pathologist should endeavor to understand one another. Each of the three must include in his intellectual equipment much possessed by the

other two. In this manner, and subject to its inherent limitations, the study of microscopic changes in the skin may prove to be of greater value than it has hitherto in clinical diagnosis.

DISCUSSION

ALFRED PLAUT: The diagnosis of infectious diseases by means of histologic study of the skin is a field in which something practical can be done. When a patient has fever and a rash, and the differential diagnosis lies between typhus and typhoid fever, one is able within twenty-four hours to make a differential diagnosis by the excision of the areola. This was done in 1913 and 1914 by Eugen Fraenkel in Hamburg, and I had an opportunity to help in part of the work. The excision is quickly done; when the patient is drowsy, one does not need any preparation. With a sharp, curved pair of scissors the excision is made; two Michel clamps are applied, and the wound heals without further treatment. The lesion of typhus is so characteristic that it is really sufficient for diagnosis. On the other hand, the typical roseola of typhoid fever is not so characteristic. But a simple trick can help in the diagnosis here. One puts the excised roseola into broth in the incubator for ten hours; then one fixes, hardens and cuts the specimen. The bacilli multiply, and large heaps of bacilli can be easily seen in the stained slide. In a number of other infectious diseases, valuable information can be obtained from excision of the skin. One of my patients with miliary tuberculosis showed many small nodules in the skin, but in one instance they proved to be an intradermal accumulation of cocci, and thus had nothing to do with the tuberculosis. One patient who died of meningitis due to Friedländer's bacillus had a peculiar hemorrhagic lesion of the skin, and it was possible to demonstrate Friedländer's bacillus in the lesion. But here one has to be careful. The fact that an organism can be demonstrated in the lesion on the skin does not necessarily mean that the lesion is due to an organism. When a boy with epidemic meningitis has a large area affected by herpes on the hand and a coccus is recovered from it, no one would think that the herpes was due to the meningococcus; it was only there by chance. A lesion on the skin seen under the microscope showed some similarity to the lesion in typhus; it was present in a case of meningitis, and clinically looked like the lesion of erythema nodosum. In two patients with doubtful clinical pictures similar to those of typhoid fever, lesions on the skin were present. One patient turned out to have typhoid fever, but the skin lesion was not quite typical. Certainly a patient with an infectious disease may have another skin lesion at the same time. In spite of such exceptions, I think that it may be really of value, especially when there is danger of an epidemic or when a ship comes from a country which is infested with typhus fever, to make excisions of the skin. The pieces can be embedded in paraffin, and all tests made within twenty-four hours.

J. J. ELLER: I should like to add one point in regard to ulcerations of the mouth and penis. Clinical diagnosis is difficult in only a few cases of ulcers of these areas. In the mouth a chronic ulcer may be due to tuberculosis, syphilis or carcinoma, and the only way in which one can make a reasonably positive diagnosis is by studying sections microscopically. A section should be taken close to the border, because if it is not, one may make an incorrect pathologic diagnosis of granulation tissue, which means nothing; the same thing applies to ulcers of the penis. Chronic penile ulcers may be due to syphilis, tuberculosis, carcinoma or granuloma inguinale. It is important here, also, to take the section along with what is apparently a small piece of healthy tissue in order to have a fair chance of getting a correct diagnosis by microscopic study.

PAUL KLEMPERER: It might be interesting to mention a case of mild typhus known as Brill's disease, in which I found the characteristic lesions of typhus.

HARRISON S. MARTLAND: What impresses me most about Dr. Highman's paper is that as a dermatologist, he frankly admits that there are any number of skin diseases that cannot be distinguished from one another by histologic sections alone. He has not once spoken of the ubiquitous plasma cell. This is indeed an advance.

WALTER J. HIGHMAN: I do not know anything about the lesion of typhoid fever examined under the microscope; I have never seen it.

I appreciate what Dr. Eller said, but I mentioned that diagnosis of tumor is the one instance in which one is more certain of the diagnosis under the microscope than clinically, and I did not think that the details concerning tumors or the aforementioned plasma cells, which have been so widely press-agented, would be interesting.

A DIFFERENTIAL SILVER STAIN. GEORGE F. LAIDLAW.

Slides were exhibited showing that in normal skin fixed in Bouin's fluid (glacial acetic acid, 20; solution of formaldehyde, 100; saturated solution of picric acid, 300), the stain differentiates the epithelial cells from the cells of mesodermic origin. Surface epithelia and the epithelia of the hair follicles and of the sebaceous and sweat glands are silver positive. Fibroblasts, smooth muscle cells and the endothelia lining the vessels are invisible; they are silver negative. Collagen is purple or red; the argyrophil reticula remain outlined in black.

Tumor cells retain the silver-positive or silver-negative features of the cells from which they spring. In papilloma, adenoma and epithelioma, the epithelial cells are positive; the fixed mesodermal cells of the interstitial tissue are silver negative. In fibroma, lipoma, angioma and myoma, all cells are negative.

Sarcoma presents a further differentiation which agrees with Ménétrier's classification of sarcomas as sarcoma of the structural tissues and sarcoma of the blood-forming organs. The cells of the structural tissues, fibrous tissue, bone, smooth muscle and vessel endothelia are silver negative; fibrosarcoma, angiosarcoma and osteogenic sarcoma are silver negative also. In the blood-forming tissues, the bone marrow, the spleen and the lymphatic tissue, the parenchyma cells are silver positive; and the tumors arising from them are silver positive also. The cells of metastases retain the features of the primary growth.

Tissue fixed in solution of formaldehyde presents this differentiation, but not so constantly. There is a curious and constant difference between the two fixatives. In epithelia fixed in Bouin's fluid, the cytoplasm stains but the nuclei remain colorless; in cells fixed in solution of formaldehyde, the nucleus takes the stain but the cytoplasm is colorless.

TECHNIC

1. Fix the sections in Bouin's fluid for three days.

2. Embed in paraffin or celloidin, or make frozen sections.

3. Stick paraffin sections on the slide with Masson's gelatin glue and harden in hot solution of formaldehyde fumes; otherwise, they float off in the hot alkaline silver.

4. After removal of the paraffin, wash in running water for twenty minutes to remove the picric acid.

5. Mordant with the Mallory bleach: (*a*) 1 per cent tincture of iodin, three minutes; rinse in tap water; (*b*) 5 per cent sodium hyposulphite, three minutes; rinse in tap water; (*c*) 0.25 per cent potassium permanganate, three minutes; rinse in tap water; (*d*) 5 per cent oxalic acid, three minutes; wash well in running water for ten minutes.

6. Immerse in distilled water; change three times within five or ten minutes to insure clean slides entering the silver solution.

7. Del Rio-Hortega's lithium silver augmented to 10 per cent.

Heat the stock solution in the oven to 50 C. and stain in the oven for five minutes. As an economic measure, the same silver solution may be used many times, being filtered before use.

8. Rinse with distilled water.

9. Solution of formaldehyde, 1 per cent; flood the slides several times for five minutes.

10. Rinse with distilled water.

11. Immerse in yellow gold chloride, 1:500, at room temperature for ten minutes; the gold solution may be used many times until it becomes pale.

12. Rinse with distilled water.

13. Pour oxalic acid, 5 per cent, on slide and leave for ten minutes.

14. Rinse with distilled water.

15. Pour sodium hyposulphite, 5 per cent, on slide and change as often as it becomes turbid for ten minutes.

16. Wash well in running water for ten minutes. Counterstain if desired and mount in balsam.

Masson's Gelatin Glue.—Dissolve a bit of sheet gelatin 0.5 cm. square in 20 cc. of distilled water, warming over the flame. Place a row of clean slides on the warm plate at 45 C. Filter a large drop of gelatin solution on each slide and float the section on it. When the section spreads, stand the slide upright to drain, blot with absorbent paper and place immediately in the 45 C. or 50 C. oven, leaving an open dish of solution of formaldehyde in the oven. In thirty minutes, the sections are ready for staining with hematoxylin or the aniline dyes; for silver staining, it is better to leave the sections in the hot solution of formaldehyde vapor for several hours or overnight.

Ten Per Cent Lithium Silver (Modified Hortega).—To make 120 cc. in a 250 cc. glass stoppered graduate, dissolve 12 Gm. of silver nitrate, chemically pure, in 30 cc. of distilled water. Add 220 cc. of saturated solution of lithium carbonate, chemically pure, in distilled water. Shake well; let settle to about 70 cc. of precipitate; wash well with distilled water three or four times. After it has settled to about 70 cc. of precipitate, decant the wash water and add aqua ammoniae fortior, shaking constantly until the fluid is almost clear. Add distilled water to 120 cc., shake and filter into a brown glass-stoppered stock bottle. The solution keeps for many months; it is so strong that a slight precipitate of silver is negligible. Ordinary filter paper is apt to turn brown and discolor the solution while filtering. Use Whatman filter paper no. 40 or 42 or Schleicher and Schüll, no. 589.

This technic is a modification of Del Rio-Hortega's connective tissue stain, which has been popularized in this country by Foot. The writer's modifications are the increase of the silver to 10 per cent; the use of the Mallory bleach as a mordant for silver on tissue fixed in Bouin's fluid, and the intercalation of oxalic acid between the gold and the sodium hyposulphite. A more detailed account of the technic appears in the *American Journal of Pathology* for May.

DISCUSSION

ALFRED PLAUT: How does the nevus cell act?

GEORGE F. LAIDLAW: Silver differentiates two kinds of nevus cells which, in a general way, agree with Masson's hypothesis of a double origin, the one from the Schwann cells and the other from the epithelium. As Masson pointed out, the common nevus cells occur in the form of clusters and nucleated bands enclosed in a thin sheath of collagen. These cells are silver negative like the Schwann cells from which they are supposed to be derived. In the upper part of many nevi are found larger cells resembling epithelia or spindle and stellate forms like chromatophores; these cells are supposed to spring from the epithelium and, like the epithelia, they are silver positive. Further than this, I have not gone.

PAUL KLEMPERER: I wish to express my admiration for this work, because I feel that it is full of possibilities for the pathologist. If it actually works and, knowing Dr. Laidlaw, I have no doubt that it will, it will give us an opportunity to decide several morphologic questions which so far it has not been possible to settle. For instance, the origin of the small thymic cells can be decided, whether mesenchymal or epithelial in nature. It will be possible to decide whether the so-called alveolar epithelium of the lung is actually epithelial or mesenchymal in nature. I think that the work is of the greatest importance and that it should

be taken up at once in the laboratories. There is one question I should like to ask. Among the skin sections, I missed a tumor which is one of those that has given rise to much discussion: the so-called endothelioma. I am sure that Dr. Laidlaw has had the opportunity to see a tumor of this type, and I would be interested to know whether this method confirms the belief held today that the so-called endotheliomas of the skin are epithelial in origin. I would like to ask about the behavior of the reticulum cell; is it positive to silver?

H. S. MARTLAND: I feel the same as Dr. Klemperer does about Dr. Laidlaw's painstaking work. Are the histiocytes of the reticulo-endothelial system positive?

GEORGE F. LAIDLAW: I am not ready to say much about endothelioma. It is a debatable subject requiring much more study and material. I have not had the opportunity to stain an endothelioma of the skin.

H. S. MARTLAND: What about the Dorothy Reed cell in Hodgkin's disease? Is it positive?

GEORGE F. LAIDLAW: Yes.

WALTER J. HIGHMAN: Have you made any comparative studies with mycosis fungoides?

GEORGE F. LAIDLAW: No.

PAUL KLEMPERER: Is it possible to use this stain with old material which has been fixed in solution of formaldehyde?

GEORGE F. LAIDLAW: Yes.

MULTICENTRIC BASAL CELL EPITHELIOMA: A POSSIBLE CLINICAL ENTITY. PAUL GROSS (by invitation).

After a brief reference to the literature, especially the work of Jadassohn and Graham Little, Henry Janeway's article on the early stages of epithelioma was mentioned as the first which associated the clinical picture of superficial basal cell epithelioma with the histologic picture of multicentric basal cell proliferation.

A short summary was given of the essential clinical features of this condition, which so frequently resembles some other superficial dermatosis. For the proper conception of histologic peculiarities, the author considered the long duration of the lesions of importance.

The trunk is the favorite location. Multiplicity is not an essential requirement for diagnosis. The clinical resemblance to Bowen's precancerous dermatosis is mentioned.

With the aid of lantern slides of sections from three patients observed by the author during the last three years, the histology was described and discussed.

The characteristics are found in multicentric epithelial budding, which is made up of undifferentiated basal cells and is usually derived and in continuity with the basal cell layer of epidermis, but in one slide an identical proliferation was demonstrated from the lower portion of a follicle.

The author was greatly interested in the frequent occurrence of slits and large spaces which surround these basal cell proliferations and are lined by dense connective tissue; but he did not feel justified in following Lipschutz, who interpreted them as preformed lymphangiectatic spaces.

Infiltration in the cutis with lymphocytes and plasma cells was found in all sections. Finally a slide was demonstrated, showing the transformation of a multicentric epithelioma into a typical reticular basal cell cancer.

In discussing the histologic observations and the interpretation by different authors, the author felt that a certain relationship, even histologically, seemed to exist to Bowen's precancerous dermatosis. The question arises as to whether both conditions are precancerous or true intra-epidermal cancers, and in both a nevoid preformation seems to be probable.

PULMONARY STENOSIS IN AN ADULT WITH BACTERIAL ENDOCARDITIS. LOUIS FAUGERES BISHOP, LOUIS FAUGERES BISHOP, JR., and S. G. WALLACE (by invitation).

History.—A woman, aged 32, was seen first on March 12, 1925. She stated that she had always suffered from dyspnea on exertion which for the past year had increased in severity. She also suffered from asthenia and insomnia.

She gave a history of measles, mumps, chickenpox, pneumonia and severe scarlet fever in childhood. She was reported to have had heart trouble at 1 year of age. At 14 years of age she had "rheumatism." She had a chronic cough, but no expectoration or hemoptysis. Her appetite had always been poor. The menstrual history was irregular. Her marital history disclosed one normal pregnancy; her husband died of tuberculosis.

Physical Examination.—The patient, a blond, was thin and pale. The veins of the neck were distended. The heart was moderately enlarged; the apex was visible outside the nipple line, with marked visible apical pulsation and definite thrill over the mitral area. The cardiac rhythm was regular; the rate was 92. A loud, blowing systolic murmur was heard over the entire precordium, most marked over the pulmonic area, transmitted to the left, and an occasional presystolic murmur was heard over the mitral area. The blood pressure was systolic 110, diastolic 70. The liver was palpable 2 fingerbreadths below the costal margin.

The blood count showed 6,300,000 red blood cells; hemoglobin, 70 per cent; white blood cells, 8,000. The blood chemistry was normal. The Wassermann test of the blood was negative. The urine showed nothing.

The electrocardiogram showed a normal sinus rhythm; normal conduction time, and a marked right ventricular preponderance; the P wave was abnormally large; there was an inverted T wave in leads II and III.

Course.—In 1927 the patient went to California and led a restful, outdoor life, but her cardiac reserve decreased. She returned in February, 1928, with increased dyspnea, rapid pulse, nervousness and a hacking cough. Examination in March, 1928, showed that the spleen and liver were palpable, and they became enlarged progressively in spite of continued rest at resorts. In September, 1928, she returned to New York. On examination, the mucous membranes were pale; petechiae were present in the right conjunctiva; the spleen was palpable almost to the umbilicus, and was hard and firm; the liver was palpable 2 fingerbreadths below the costal border. The cardiac examination showed no change. The temperature ranged between 100 and 104 F. A blood count showed 3,950,000 red blood cells, 60 per cent hemoglobin and 6,500 white blood cells. A blood culture was negative. The urine showed many red blood cells and a few granular casts.

The patient became progressively more anemic and more septic. Edema appeared in the legs and vulva and spread to the back. She complained of cough, epistaxis and occasional bloody diarrhea. A purulent vaginal discharge and petechiae over the body appeared. In November, she became stuporous and irrational, and died suddenly on December 2.

Autopsy.—The pericardium bulged slightly; it contained 40 cc. of fibrinous, flaky serum; the visceral and parietal layers showed shaggy, hairlike exudate, and some easily broken adhesions. The heart weighed 260 Gm. The right chamber was greatly enlarged, the apex being formed by the right ventricle. The right auricle was markedly distended and hypertrophied. The posterior auricular wall, near the orifice of the coronary sinus, had two saccular adhesions; nodular thickenings and nodules were also found. The right ventricle was greatly hypertrophied, with marked endocardial thickening. The pulmonary valve showed long, grayish vegetations. The left ventricle appeared normal. The myocardium, on section, showed irregular areas of fibrous change. The aortic cusps showed some calcification.

The lungs were congested posteriorly, with areas of partially consolidated tissue.

The spleen weighed 900 Gm. It was a dense purplish red, cut easily, and showed many follicles and no infarcts.

The liver weighed 2,000 Gm., was dense and firm, and had a marked nutmeg appearance.

The kidneys were normal in size and were dark purple, with mucus-like dots scattered through the zone glomeruli.

The condition was diagnosed as lobar pneumonia, glomerular nephritis, chronic passive congestion of the spleen and liver, fibrinous pericarditis and myocardial fibrosis.

DISCUSSION

C. DE LA CHAPELLE: This is an interesting and unusual case, and adds another one to the list of cases of congenital pulmonary stenosis associated with bacterial endocarditis. Judging by its gross appearance, it looks like a typical lesion of *Streptococcus viridans* endocarditis. The presence, however, of fibrinous pericarditis in *Streptococcus viridans* infection is unusual, about 0.5 to 1.5 per cent of the cases being associated with a pericardial lesion. Another unusual thing about the specimen, and which is often found in this valvular type of pulmonary stenosis, is the absence of associated congenital cardiac anomalies, especially a patent interventricular septum. In this case one would expect to find none of these other congenital anomalies, because of the relatively long life enjoyed by this patient.

WILLIAM C. VON GLAHN: I have had no experience with pulmonary stenosis of the congenital type. I should like to ask what organism was recovered.

HARRISON S. MARTLAND: Could not the endocarditis in this case be best classified as subacute bacterial of the indeterminate group of Libman? Such cases are frequently complicated by a pericarditis and give the vague bacteriologic manifestations seen in this case.

LOUIS FAUGERES BISHOP, JR.: I showed this patient to Dr. Libman, who told me that undoubtedly the condition must have passed through the indeterminate stage. On what grounds he based that I am not sure. The two blood cultures were negative. A Gram-Weigert stain was made, the vegetations being crushed, which showed what looked more like a round staphylococcus than *Streptococcus viridans*. The stain was unsatisfactory, and although some care was taken with it, it was not possible to determine the organisms. I understand that one should use not only the Gram-Weigert stain, but some of the others in order to bring out the organisms.

Book Reviews

LEHRBUCH DER ENTWICKLUNG DES MENSCHEN. VON DR. ALFRED FISCHEL, O. Professor der Embryologie und Vorstand des Embryologischen Institutes der Wiener Universität. Mitt 668 Z. T. Farbigen Abbildungen. Price, 86 marks. Pp. 822. Berlin: Julius Springer, 1929.

It is well recognized that many of the earlier stages of development of man are imperfectly known. The inclusion of earlier phases of the development of lower organisms not only fills the gaps in the knowledge of human embryology but at the same time serves to simplify many of the complexities encountered in human development. It is indeed a happy combination to find a text in which the general features of development receive adequate attention. Special topics are introduced to illustrate the various ramifications of the problem, and the details of human development are combined in one attractively printed volume, replete with excellent and wisely chosen illustrations. Professor Fischel's book is one of the most successful attempts to realize these ends that has recently appeared.

The interesting 15 page introduction and historical sketch of the development of the subject of embryology is followed by a discussion of general embryology of 250 pages (part 1), and an account of human organogeny of 550 pages (part 2). The arrangement of material is excellent; the stages of development are taken from the better known animal forms; the general principles of embryology are discussed in the proper place to make a coherent story of development; the illustrations are wisely chosen and beautifully executed.

The germ cells as the logical beginning of development are treated as dynamic elements. Their morphology and development concern live cells the activities of which are conditioned by certain physiologic states within and without the cells. They have a limited life and fertilizing capacity. The atypical cells are considered, and the inter-actions of the normal gametes in zygote formation is followed for different forms. Fertilization is both a means for the transmission of parental inheritance to the new organism and a means of initiating development. Chromosome behavior, the principles of genetics, parthenogenesis, polyspermy and the physicochemical changes following initiation of development receive attention. The general problems of organization, localization, and the prospective potencies of parts take the student below the surface of mere descriptive detail. Cleavage, germ-layer formation and the early appearance of the embryo are treated in a comparative manner with many illustrations coming from invertebrates but more attention centered on an ascending series of vertebrates including the lower chordates (amphioxus), amphibia, reptilia, apes and lower mammalia. The development of such a series of individual forms leads logically to the known or hypothetic similar stages in human development. A discussion of complete and incomplete twinning in different animals, and double human monsters, serves to further demonstrate developmental capacities. The formation of the embryonic membranes and delimination of the embryos of many species is logically followed by a description of the earliest human embryos and by the problems of implantation and placentation. The description of the human membranes and placenta is again proceded by descriptions of these structures in lower mammals.

In part 1 the author has interspersed sufficient interpretation and philosophic deduction with demonstrations of fact to build up a well rounded presentation of the general features of development; the comparative development of different animal forms serves admirably to demonstrate these general features, and at the same time the account contains a great deal of detail for the development of the individual species. Under each separate topic of discussion the general development serves to introduce either the known or hypothetic condition of the develop-

ment of man. One greatly misses references to original sources, especially in part 1. A good bibliography would greatly enhance the value of the book for both the general and the special student. Many questionable statements cannot be referred to the original source for whatever special condition may have justified the statement. Some errors occur, but this is perhaps to be expected in a first edition.

Part 2 is concerned entirely with human organogeny. The development of the different germinal layers is followed from very early embryos, through the origin and development of the different organs. In some cases, more advanced differentiation of the organ substance is given, and even more attention to the later histogenesis would have been a distinct addition but perhaps beyond the scope intended for one volume. One of the more outstanding omissions of human development is that of the circulatory system, in particular the development of the postcaval system. Despite the completeness of the work of McClure and Butler (1925) on the development of the postcava in man, Fischel has illustrated the development only by schematic diagrams based on older and incomplete accounts.

The book is more complete in the general phases of development and the specific development of man than most treatises on embryology. For many it will be regretted that more attention was not given to malformations arising in embryonic development, as these find their explanations in peculiarities of development of certain parts. The most severe omission, to the special student, is undoubtedly that of a bibliography.

THE KAHN TEST—A PRACTICAL GUIDE. By R. L. KAHN, Sc.D. Price, $4. Pp. 201. Baltimore: Williams & Wilkins Company, 1928.

In presenting the technic and fundamentals of the Kahn test in a well planned volume of about 200 pages including an up-to-date bibliography, Kahn has filled a need. His earlier volume, "Serum Diagnosis of Syphilis by Precipitation" deals largely with the historical and developmental phases of the test. As such it is well supplemented by this recent book. In the first place, much of the material presented in this book will be of value to those students of serologic problems who are eager for an understanding of the fundamental principles on which the Kahn test is based. At the same time the book fills the need of the serologic worker by giving precise directions for the various procedures in dealing with serum and spinal fluid, to each of which a chapter is devoted with a brief discussion of clinical interpretation. Although there is a certain amount of repetition of detail, outline form is frequently used, and numerous illustrative and summarizing tables are included.

Of particular interest to the serologist is the chapter on antigen standardization. In connection with this problem, Kahn has made an especially significant contribution. He introduces the use of a special sensitizing lipid extract, and presents experimental evidence for the quantitative dependence of antigen sensitiveness with syphilitic serum on the proportions of two types of lipid extracts in the antigen and the total concentration of lipids present. Practical application of this observation makes possible the correction of antigens with varying degrees of sensitiveness to the uniform "standard" sensitiveness required by the Kahn test. The same principle is also used in correcting "sensitized" antigens.

In the introductory chapter, consisting of sixty-four pages of text, tables and charts, Kahn takes a novel step toward translating the detailed studies on his own test from the particular to the more general. Presented in a manner that should appeal to the colloid chemist as well as to the serologist and syphilologist, these studies are now made available as a preliminary structure on which may be built a more fundamental understanding of the nature of the serologic reaction in syphilis. The "Practical Guide" should therefore arouse interest among a varied group of workers. To the serologist, whatever his opinions on the controversial subject of serum tests for syphilis, the book will be especially valuable.

SURGICAL PATHOLOGY. By CECIL P. G. WAKELEY, F.R.C.S. (ENG.), F.R.S. (EDIN.), and ST. J. D. BUXTON, M.B., B.S. (LOND.), F.R.C.S. (ENG.). Price, $12.50. Pp. 904, with 392 illustrations. New York: William Wood & Company, 1929.

This book is intended to "put forward such an account of the pathological side of surgery as may help readers with their clinical work" and to help the undergraduate student, particularly in the study of specimens in the museums. There are seventy-five chapters dealing with a great variety of topics, ranging from bacteriology to shock, but for the most part with special descriptive pathologic anatomy. The presentation of the various subjects is brief and more in the way of succinct summaries or cataloguing of more or less generally accepted items of knowledge with avoidance of discussion of underlying principles, conflicting theories and unsettled questions. In many cases the chapters are so brief as to be of little significance except possibly by way of introduction to more comprehensive discussions. This is true particularly of the chapters dealing with bacteriology, infection and immunity, which consist of nine pages; inflammation, of eight pages; wounds, of five pages; erysipelas, of one-half page and tuberculosis of six pages. Giant-cell tumors of the bone are described (too briefly) under the name of myeloma, and the statements in the two places in which these growths are considered do not agree. Myeloma as ordinarily understood is discussed under the term myelomatosis. So-called carcinoid of the appendix, carcinoma of the prostate, melanoma and endometriosis are mentioned merely as examples of conditions that are not described fully enough. For the most part the illustrations are well selected, and many of them are original. A large number is credited to the *British Journal of Surgery*. In the case of figures 91, 92 and 93 it is not possible to discover the letters referred to in the descriptive legends. The book will be of use as a guide in the laboratory and museum, but it in no sense can take the place of standard works on pathology. The most valuable part lies in the illustrations.

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